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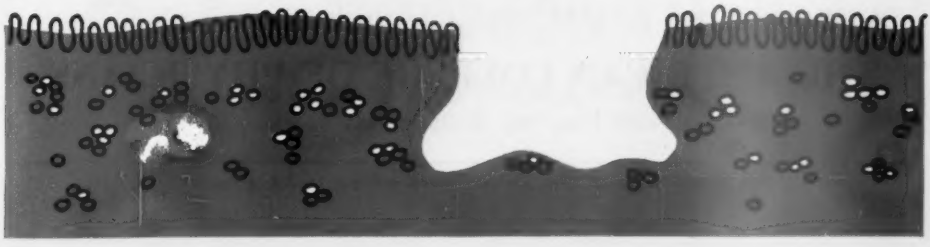

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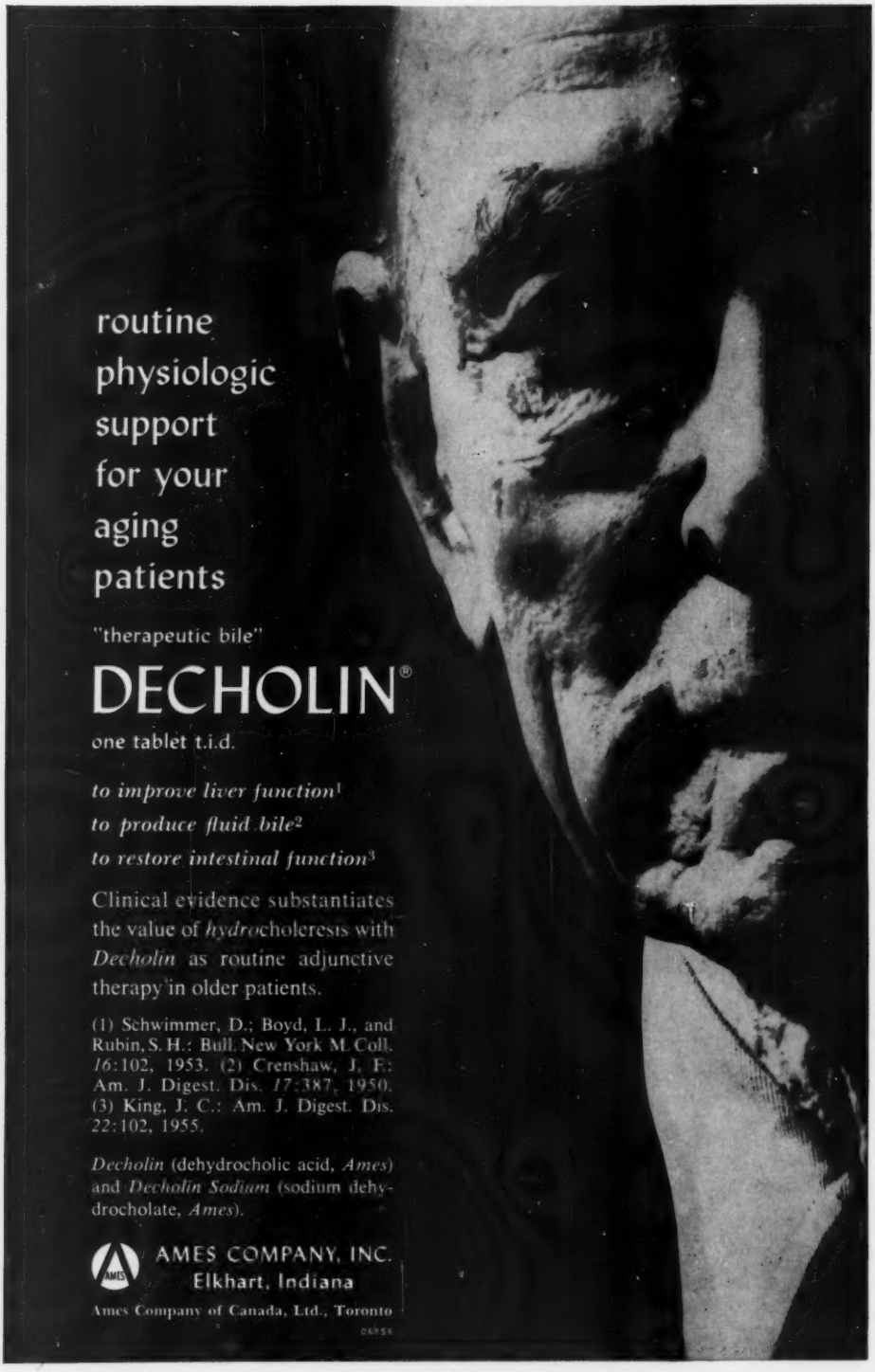
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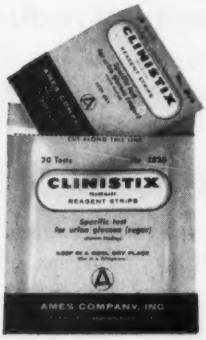

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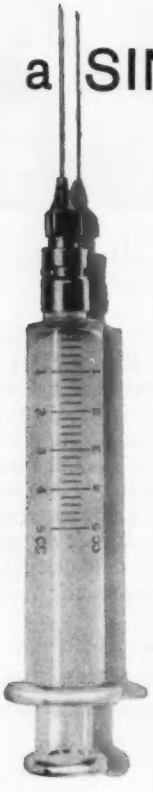

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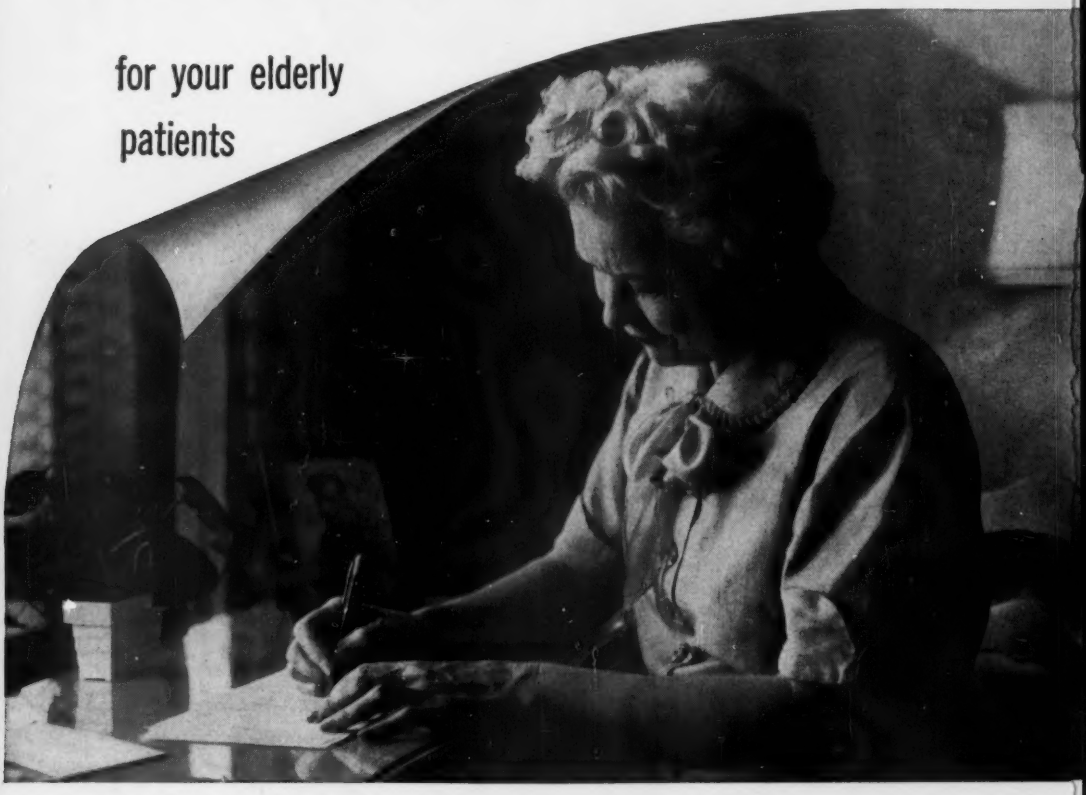

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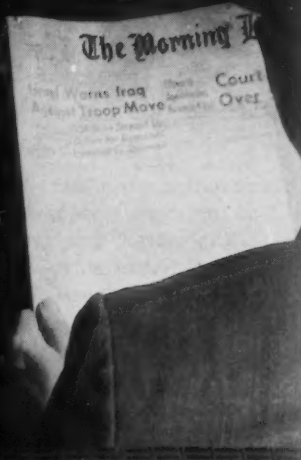


THROUGH THE DAY

THROUGH THE NIGHT

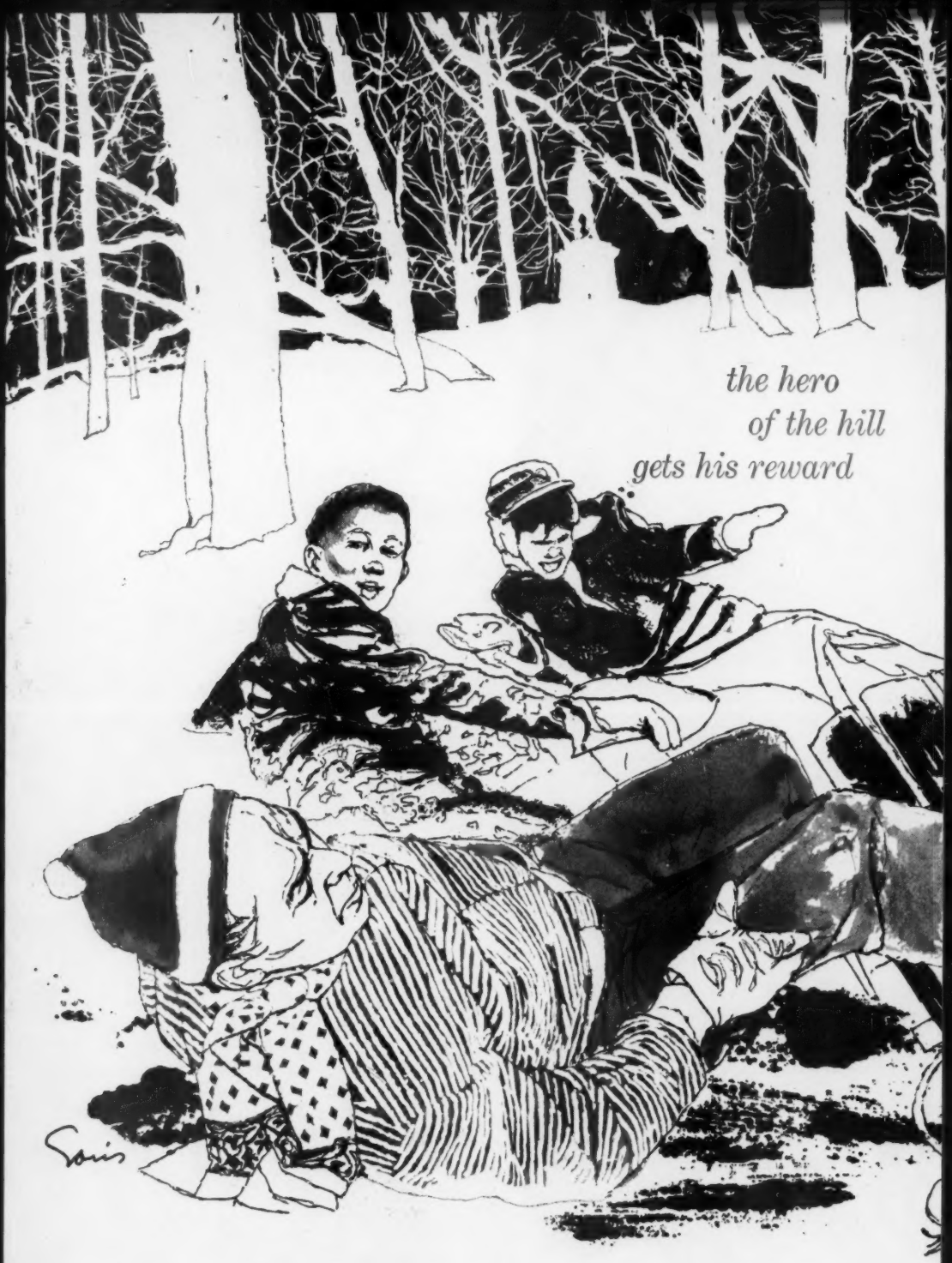
Expectorant action
Antihistaminic action
Sedative action
Topical anesthetic action

PHENERGAN

EXPECTORANT

Promethazine Expectorant with Codeine Plain (without Codeine)

Wyeth®
Philadelphia 1, Pa.



PT.M. 20-J-117

charleyhorse!

The pain Dad feels now is the beginning of tenosynovitis. With adequate early treatment he'll be able to stay on his job. Delaying therapy might result in the development of effusion and, later, calcification of ligaments or even periarthritis with severe pain and serious restriction of movement.

Immediate antirheumatic therapy is to be encouraged in the treatment of tenosynovitis, as it should be in the majority of other common rheumatic disorders, to alleviate pain and prevent progression of the disturbance to a point of irreversible damage.

SIGMAGEN provides doubly protective corticoid-salicylate therapy—a combination of METICORTEN® (prednisone) and acetylsalicylic acid giving additive antirheumatic benefit as well as rapid analgesic effect. These benefits are supported by aluminum hydroxide to counteract excess gastric acidity and by ascorbic acid, the vitamin closely linked to adrenocortical function, to help meet the increased need for this vitamin during stress situations.

for patients who go beyond their physical capacity

protective corticoid-salicylate therapy

SIGMAGEN

corticoid-analgesic compound **Tablets**

Schering

THE CASE FOR EARLY CONTROL OF HYPERTENSION[1]

In the Guest Editorial for GP in July, Dr. Edward D. Freis reexamines two major questions:

1. Should Hypertension Be Treated Early?

Freis finds the case for early treatment to rest on cause-and-effect evidence: "... high pressure, ... *and nothing else but this high pressure,* creates many if not all the organic manifestations that lead to the final disability and eventual death of the patient." The "evidence presents a cogent argument for the treatment of hypertension early before vascular damage has occurred."[1]

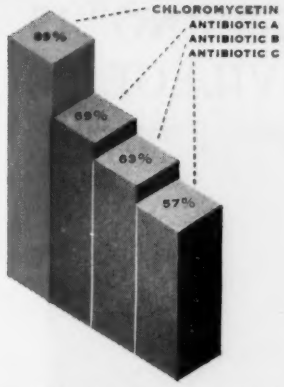
2. What Is the Role of the More Potent Agents? "... the evidence ... suggests that the technique [for the effective and safe use of such agents as ANSOLYSEN] should be more widely learned and employed. Furthermore, ... the patients with early hypertension, especially those without renal damage, are far more easily controlled, with fewer side effects, than the patients with advanced hypertension."[1]

Freis cautions that these views are not presented as dogma; "... they have been developed to show the other side of an argument that seems to have many points in its favor."[1]

1. Freis, Edward D.: Guest Editorial. GP *14*:72 (July) 1956.

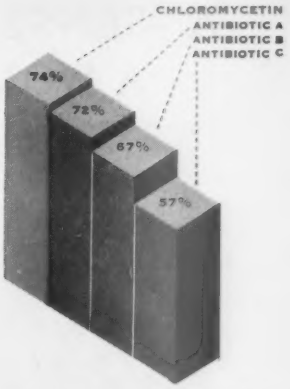
ANSOLYSEN®
TARTRATE **Pentolinium Tartrate**
Lowers Blood Pressure

Wyeth®
Philadelphia 1, Pa.



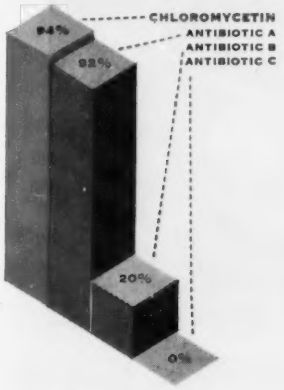
NONHEMOLYTIC MICROCOCCUS AUREUS

(363-418 STRAINS)



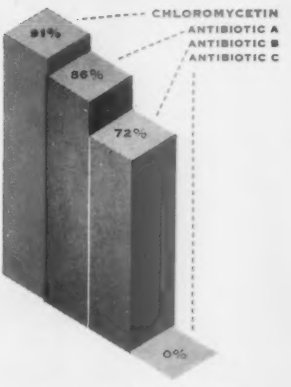
HEMOLYTIC MICROCOCCUS AUREUS

(729-776 STRAINS)



ESCHERICHIA COLI

(478-596 STRAINS)



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(153-193 STRAINS)

greater antibacterial efficacy...

Chloromycetin®

for today's problem pathogens

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

*This graph is adapted from Altemeier, W. A.; Culbertson, W. R.; Sherman, R.; Cole, W.; Elstun, W., & Fultz, C. T.: *J.A.M.A.* 157:305 (Jan. 22) 1955.

PARKE, DAVIS & COMPANY

DETROIT 32, MICHIGAN

A "SENSE OF WELL-BEING" IS A WOMAN'S PRIVILEGE

Every woman who suffers in the menopause deserves "Premarin."

Relief from distressing symptoms is promptly obtained and a "sense of well-being" is an extra benefit of therapy.

"Premarin" presents the complete equine estrogen-complex. Has no odor, imparts no odor. Available as tablets or liquid.

"PREMARIN"®
Conjugated estrogens (equine)

in the menopause and the pre- and postmenopausal syndrome

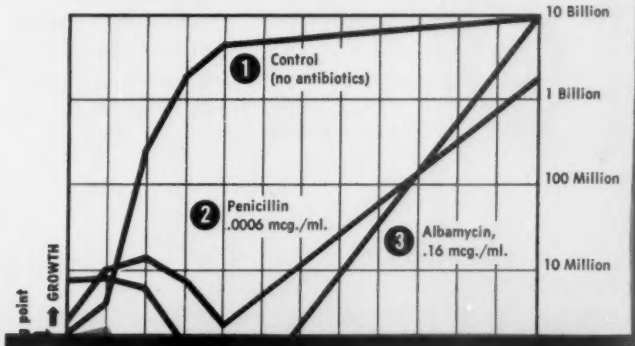
Ayerst LABORATORIES • New York, N. Y. • Montreal, Canada

5644

Antibiotic Synergism

This graph shows the growth rate of a penicillin- sensitive strain of Staphylococcus (Micrococcus pyogenes, var. aureus) under 3 conditions:

1. In the absence of antibiotics
2. In the presence of subinhibitory concentration of penicillin
3. In the presence of subinhibitory concentration of Albamycin*



Now lift this transparency and see what happens when **half** these amounts of **penicillin** and Albamycin are **combined!**

Upjohn

*Trademark, Reg. U.S. Pat. Off.—The Upjohn brand of crystalline novobiocin sodium.
Data: Upjohn Research Laboratories (3265—ARB—119)

Antibiotic Synergism

This graph shows the growth rate of a penicillin- sensitive strain of Staphylococcus (Micrococcus pyogenes, var. aureus) under 3 conditions:

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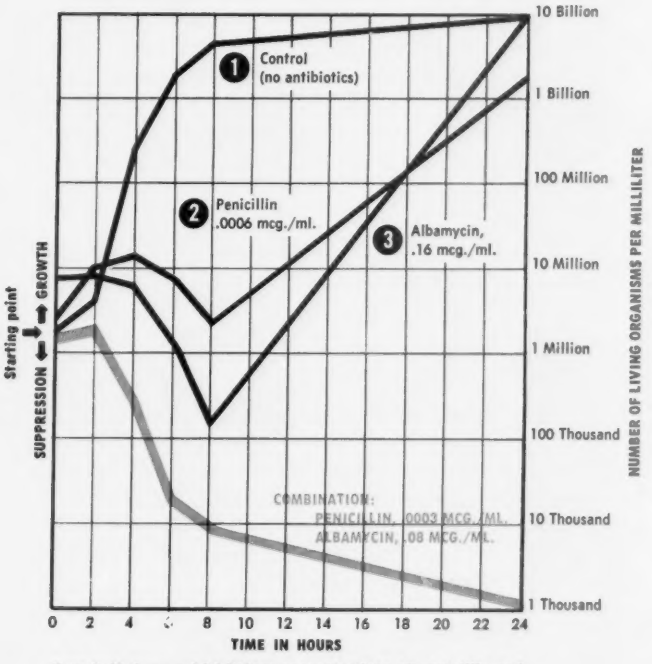

Even half these subinhibitory concentrations of penicillin and Albamycin, when combined, produce a dramatic bactericidal effect.

Such a product is available now

Upjohn

*Trademark, Reg. U.S. Pat. Off.—The Upjohn brand of crystalline novobiocin sodium.
Data: Upjohn Research Laboratories (3265—ARB—119)

average dosage only t.i.d.

New

Alba-Penicillin*

(Albamycin plus penicillin)

Compare it with the antibiotic you are currently using:

Range of effectiveness: Alba-Penicillin is effective against the organisms that cause the overwhelming majority of bacterial infections (Staphylococci, Streptococci, Pneumococci, Proteus).

Risk of resistance: Because in vitro tests show this combination is synergistic against even Staphylococci **already** resistant to all other antibiotics, the risk of resistance is minimized.

Risk of enterocolitis: Because it has little or no effect on the predominant Gram-negative intestinal bacteria, and is highly effective against Staphylococci, there is virtually no danger of enterocolitis due to alteration in intestinal flora, or of other side effects such as perianal pruritus.

Convenience: Alba-Penicillin is oral therapy, and the average adult dosage is only **1 to 2 capsules t.i.d.**, which eliminates middle-of-the-night medication.

It is available in bottles of 16 capsules. Each capsule contains 250 mg. Albamycin (as novobiocin sodium, crystalline) and 250,000 units penicillin G potassium.

Upjohn

The Upjohn Company • Kalamazoo, Michigan

*Trademark

"...Well, I always prescribe Rorer's Maalox. It's an excellent antacid, and patients will take it indefinitely."

. . . . . .

MAALOX® suspension, bottles of 12 fluidounces (*sample on request*); tablets, bottles of 100.

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the "reducer"

happy

'Methedrine'

brand Methamphetamine Hydrochloride

'Methedrine' dispels abnormal craving for food, and subtly elevates the mood. Reducing diets are accepted easily, without frustration.

'Methedrine' is safe, in recommended doses, for pregnant women.

'Methedrine' brand Methamphetamine Hydrochloride Tablet of 5 mg., scored.

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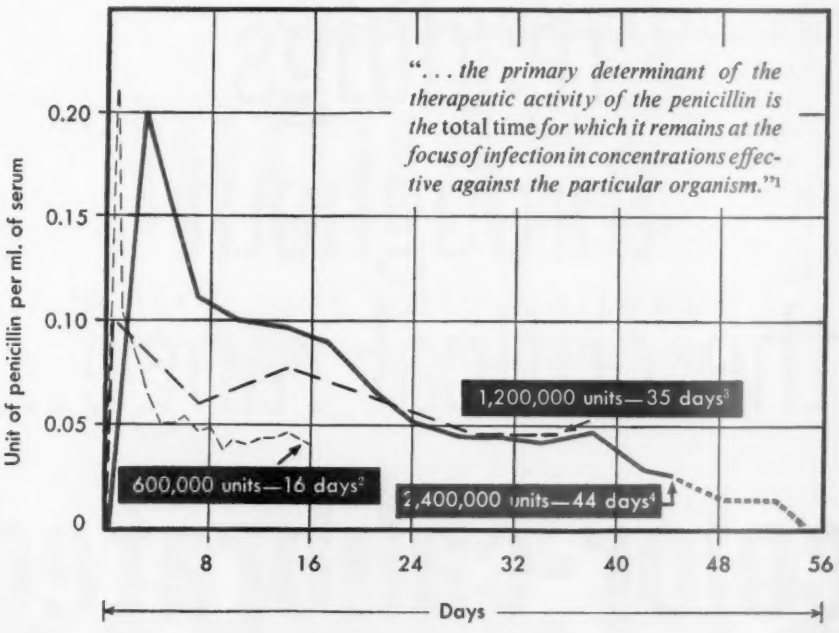
PROLONGED ACTION

BICILLIN BLOOD LEVELS—ONE INJECTION



Injection BICILLIN is unique for its persistence of penicillin action. "When injected intramuscularly, it remains in the blood longer than any other available penicillin preparation."[2] In both prophylaxis and treatment, it offers lethal duration and concentration —effective against a wide variety of penicillin-responsive infections.

- Streptococcal infections
- Rheumatic fever (prophylaxis)
- Pneumococcal infections
- Gonorrhea
- Syphilis (primary and secondary)
- Surgical infections

1. Eagle, H., et al.: J. Lab. & Clin. Med. *41*:122 (Jan.) 1953. 2. Welch, H., et al.: Antibiot. & Chemo. *3*:1053 (Oct.) 1953. 3. Stollerman, G.H., and Rusoff, J.H.: J.A.M.A. *150*:1571 (Dec. 20) 1952. 4. Welch, H., and Putnam, L.E.: Personal communication.

Wyeth®
Philadelphia 1, Pa.

INJECTION BICILLIN® LONG-ACTING

Benzathine Penicillin G (Dibenzylethylenediamine Dipenicillin G)

Penicillin with a Surety Factor

distinctive readings throughout the critical range...

color-calibrated CLINITEST®

BRAND

the urine-sugar test with the standardized, laboratory-controlled color scale

- full color calibration for the urine-sugar spectrum
- easily read, firmly established blue-to-orange scale
- sharp color distinction between readings

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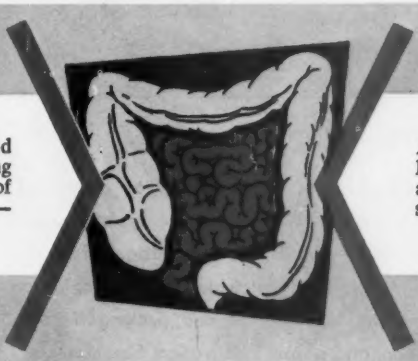
At last! **a nutritive deconstipant**

MODANE

which not only relieves but also rehabilitates



Improves peristalsis and bowel movement, suggesting a selective stimulation of the intrinsic nerve plexus—not irritation.

Acts as a laxative on the large bowel only—does not affect motor activity of the small bowel.

Actually, a *therapeutic* approach . . . relief plus repair for the atonic bowel.

Acts surely, gently, overnight — without griping. Non-toxic, non-habit-forming.

Provides Pantothenic Acid — proven indispensable to acetyl-choline formation and normal bowel function.

Each tablet of MODANE REGULAR contains Danthron 75 mg. and Calcium Pantothenate 25 mg., Danthron to encourage peristalsis, Calcium Pantothenate for rehabilitation of the atonic bowel.

Dosage. . . . MODANE REGULAR — one tablet after the evening meal. MODANE MILD (half strength, for hypersensitive, pregnant, pediatric and diet-restricted patients) — one pink tablet after the evening meal. MODANE LIQUID (one teaspoonful equals one Modane Mild tablet) — fractional or full teaspoonful, after the evening meal.

THE WARREN-TEED PRODUCTS COMPANY
COLUMBUS 8, OHIO

WARREN-TEED *Pharmaceuticals*

4:1

A ratio for antacid action without systemic disturbance

• In hyperacidity • In peptic ulcer

Many physicians think of ALUDROX as a *prudent* antacid because it is balanced for therapeutic response and physiological protection. This is the advantage of the ALUDROX formula—a 4:1 combination of aluminum hydroxide and milk of magnesia. It provides prompt and prolonged buffering, demulcent action, and pepsin inactivation. Simultaneously, it offers defense against constipation, acid rebound, and alkalosis. Now—peppermint-flavored!

SUSPENSION TABLETS

ALUDROX

Aluminum Hydroxide with Magnesium Hydroxide

to neutralize, not penalize

Wyeth

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here are three patients who will probably be helped by weight reduction:

the hypertensive

the pregnant

the diabetic

You will find 'Dexedrine' most useful for controlling appetite in these patients during the weight reducing regimen. Numerous studies indicate that 'Dexedrine' can be used safely in the vast majority of such patients. If you have any doubts, write to us and we will send you the pertinent reprints and abstracts.

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DEXEDRINE*

dextro-amphetamine sulfate, S.K.F.

Tablets · Elixir
Spansule† capsules

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†T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F. Patent Applied For

"DOCTOR, have you tried new Carnation Instant?"

YOU'LL DISCOVER WHY THIS EXCLUSIVE CRYSTAL FORM OF NONFAT MILK HELPS YOUR PATIENTS "STAY WITH" A DIET...IT TASTES SO GOOD!

DELICIOUS FOR DRINKING: These remarkable crystals burst into fresh flavor nonfat milk instantly, even in ice-cold water. Ready to drink. Delicious for drinking. Then, too, it is easy to add extra crystals (1 tablespoon per glass, ⅓ cup per quart) for flavor far richer than bottled nonfat milk–and 25% more nonfat milk nutrients. Patients who resist ordinary nonfat milk enjoy self-enriched Carnation Instant.

MAINTAINS "WELL-BEING": Enjoyed with and between meals. Carnation Instant goes a long way in helping your patients "stay with" a diet. Provides lactose and protein to help maintain blood sugar level, keep energy up. Helps allay fatigue and the simple hunger pangs that make it hard to resist forbidden snacks.

WHY NOT try new Carnation Instant yourself? A fine, protective "boost" for the busy physician. Ready instantly, fits into your most crowded professional day.

For bacterial infections—

Gantricillin-300 Roche—

Advantages: 0.5 Gm Gantrisin plus 300,000 units penicillin in a single tablet...hence high potency...wide spectrum...convenient therapy...no likelihood of secondary fungus infections or renal blocking.

Limitations: There may be failures due to resistant strains... the usual precautions in penicillin-sulfonamide therapy should be observed.

Gantricillin®; Gantrisin® -- brand of sulfisoxazole

For troubles* that are only skin deep

(but very real to the patient)

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Cream

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Stops itching... soothes... heals

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Dry, scaly skin
Chafing
Diaper rash
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Pruritus ani, vulvae
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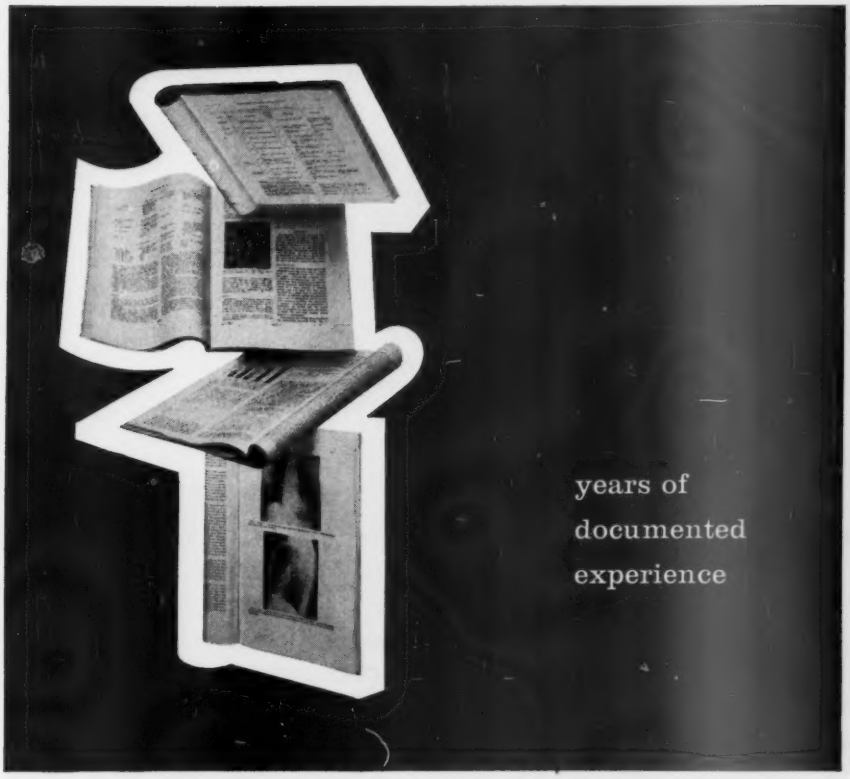
Minor burns
Bedsores

Contains vitamins
A, D, E, and *d*-Panthenol
in a non-sensitizing
vanishing cream type base
which will please the
most fastidious patients.

ROCHE *Original Research in Medicine and Chemistry*



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Practicing physicians know that many years of clinical and laboratory experience with any medication are the only real test of its efficacy and safety.

Among available, effective diuretics, the organomercurials have behind them over three decades of successful clinical use. Their clinical background and thousands of reports in the literature testify to the value of the organomercurial diuretics.

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NEOHYDRIN
BRAND OF CHLORMERODRIN (10.3 MG. OF 3-CHLOROMERCURI-2-METHOXY-PROPYLUREA EQUIVALENT TO 10 MG. OF NON-IONIC MERCURY IN EACH TABLET)

LAKESIDE

a standard for initial control of severe failure
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BRAND OF MERALLURIDE INJECTION

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ANEMIA...

Evidence shows that practically every menstruating female is in a state of precarious iron balance. Thus the iron deficiency state, due to even *normal* menstrual losses, is an extremely common occurrence.[1, 2]

Correction of this iron deficiency state results in real benefits to the tired, rundown female patient.

Strikingly superior clinical responses in menstrual anemia have been reported with RONCOVITE.[3] These results can be explained by the increased absorption and utilization of iron due to the improved bone marrow activity provided only by RONCOVITE.

Roncovite Tablets (*in menstrual anemia*):

Maximum Adult Dosage: One tablet after each meal and at bedtime.

Bottles of 100 tablets.

Literature available to physicians on request.

Roncovite®

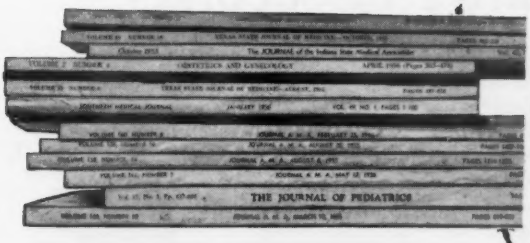
THE ORIGINAL, CLINICALLY PROVED COBALT-IRON PRODUCT

"The average female

is borderline

iron deficient..."[3]

IN MENSTRUAL



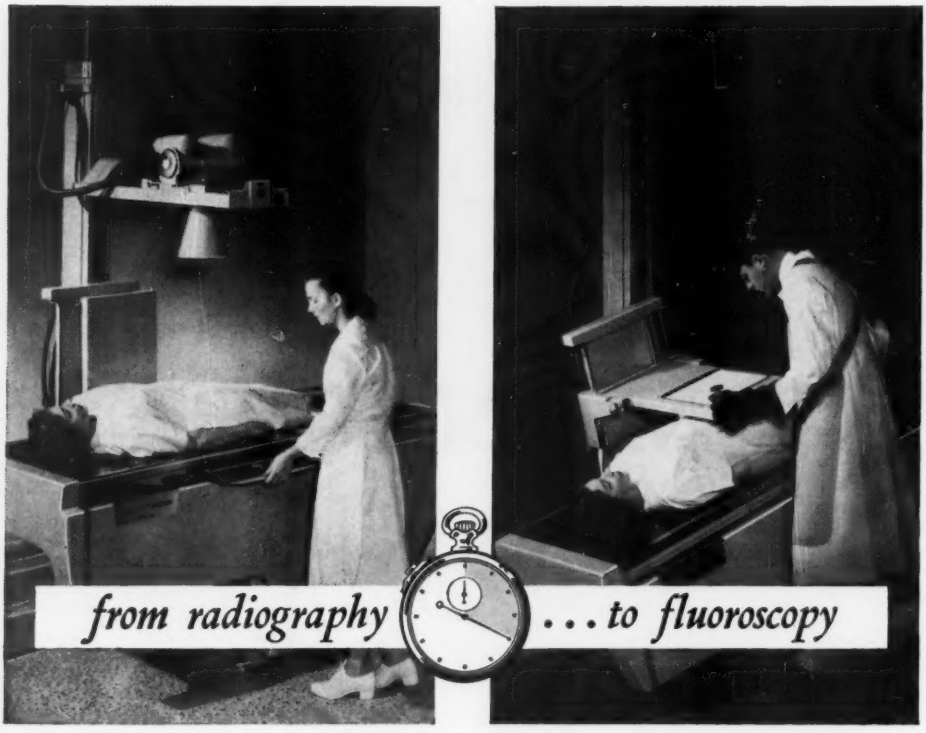
The bibliography specifies

1. Moore, C.V., and Dubach, R.: J.A.M.A. 162:197 (Sept. 15) 1956.
2. Holly, R.G.: Obstet. and Gynec. 2:124 (Aug.) 1953.
3. Ausman, D.C.: Journal-Lancet 76:290 (Oct.) 1956.

LLOYD *Brothers, Inc.*

Cincinnati 3, Ohio

PATRICIAN / *a General Electric product in step with your progress*



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'Roche'

For round-the-clock therapy

With two doses a day

Lipo Gantrisin 'Roche'—a new, palatable liquid for antibacterial therapy—offers three significant features:

1. Only two doses a day needed in most cases
2. Adequate twelve-hour blood levels after a single dose
3. Same therapeutic advantages as Gantrisin 'Roche'

Lipo Gantrisin® Acetyl—brand of acetyl sulfisoxazole in vegetable oil emulsion

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Conditions requiring diuretic treatment for sustained periods of time can be ideally controlled by DIAMOX.

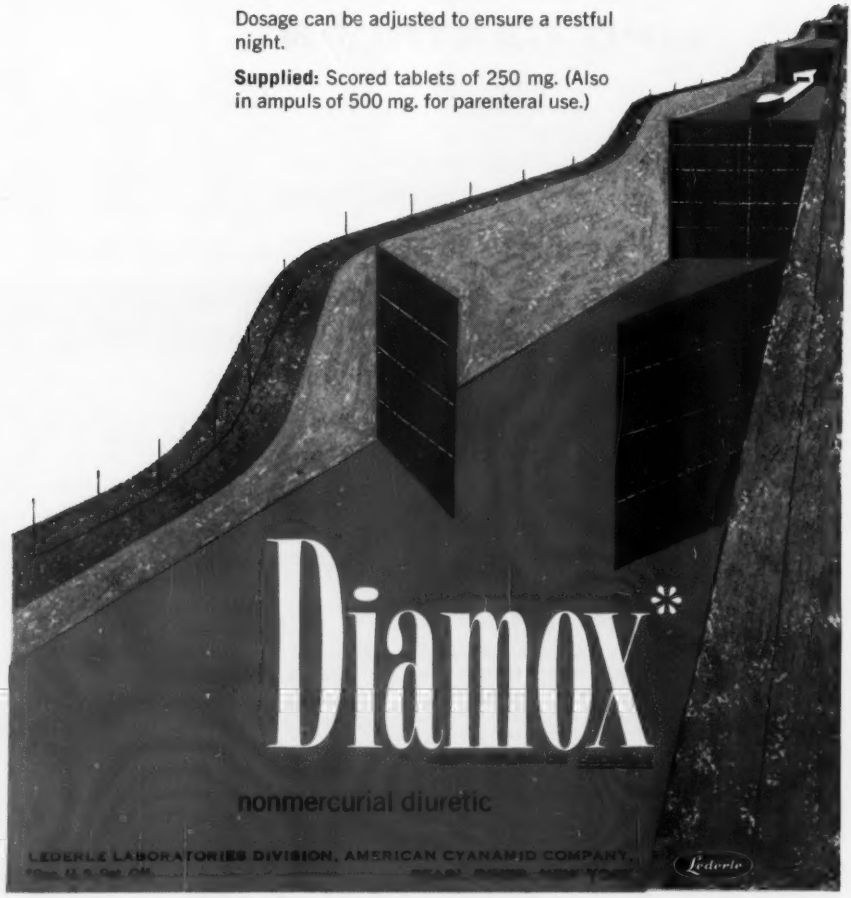
DIAMOX has been found strikingly effective in a variety of conditions: cardiac edema, glaucoma, epilepsy, toxemias of pregnancy, obesity, premenstrual tension.

Administration of DIAMOX once daily or every other day results in adequate control of edema since DIAMOX is effective in the **mobilization** of edema fluid and in the **prevention of fluid accumulation.**

A versatile diuretic, DIAMOX is well-tolerated orally, and even when given in long term dosage, side effects are rare. Excretion by the kidney is usually complete within 12 hours with no cumulative effects.

Dosage can be adjusted to ensure a restful night.

Supplied: Scored tablets of 250 mg. (Also in ampuls of 500 mg. for parenteral use.)

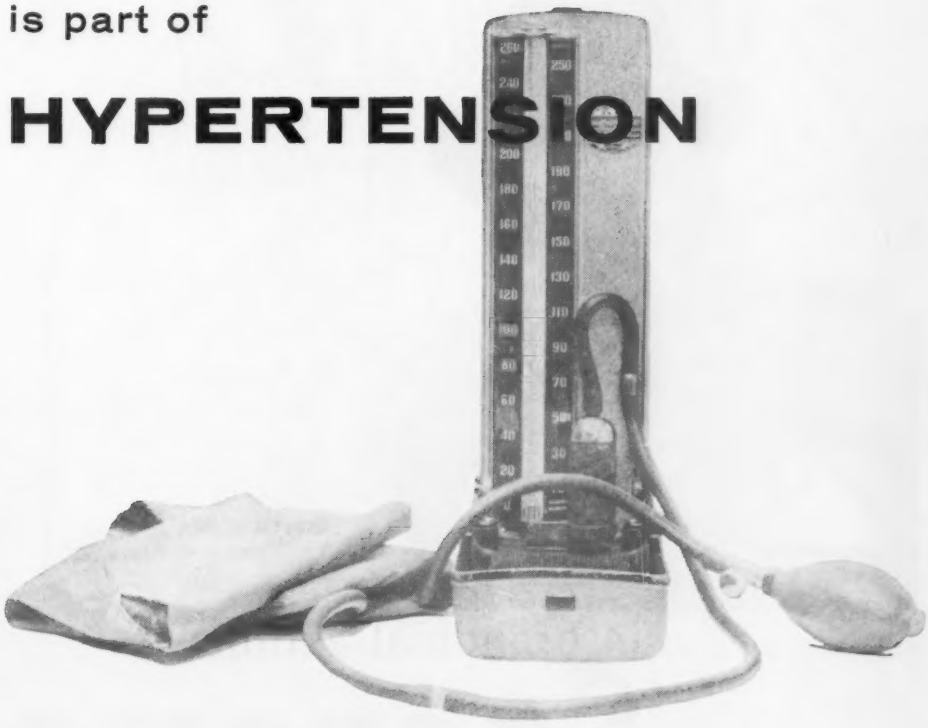


...part of *every illness*

ANXIETY

is part of

HYPERTENSION



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MEPROBAMATE

(2-methyl-2-n-propyl-1,3-propanediol dicarbamate)

Licensed under U.S. Pat. No. 2,724,720

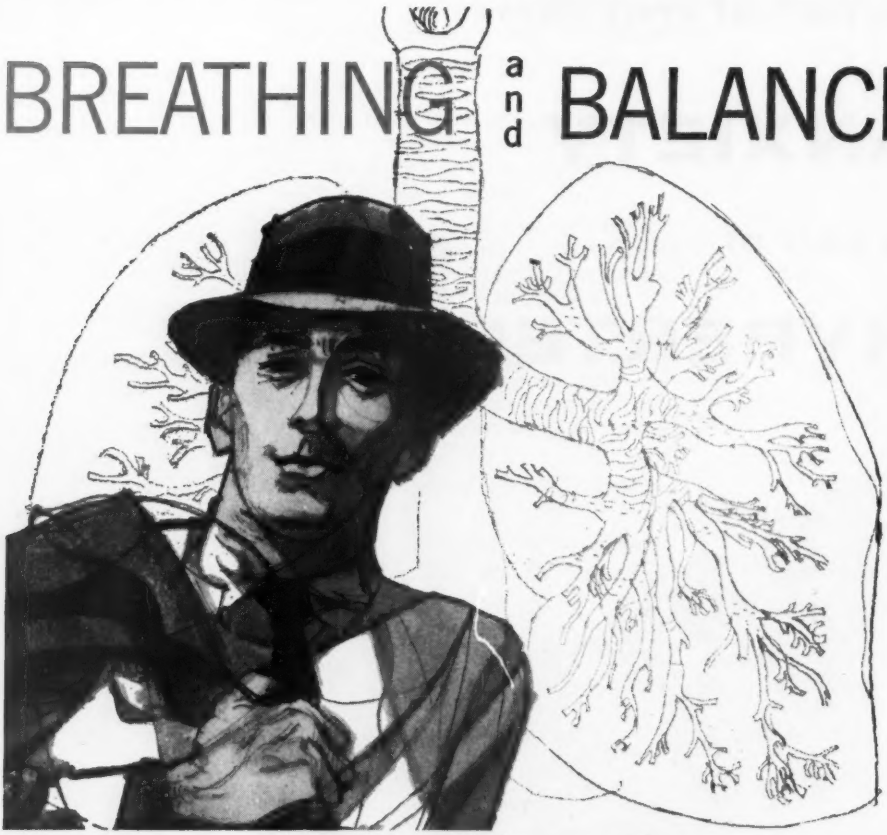
anti-anxiety factor with muscle-relaxing action

In every patient . . .
a valuable adjunct
to the customary therapy

Supplied: Tablets, 400 mg., bottles of 50.
Usual Dose: 1 tablet, t.i.d.

Wyeth®
Philadelphia 1, Pa.

BREATHING and BALANCE



in bronchial asthma

Sterane®

brand of prednisolone

whenever corticosteroids are indicated

provides restoration of breathing capacity — Relief of symptoms [bronchospasm, cough, wheezing, dyspnea] is maintained for long periods with relatively small doses.*

minimal effect on electrolyte balance — "in therapeutically effective doses . . . there is usually no sodium or fluid retention or potassium loss."* Lack of edema and undesirable weight gain permits more effective therapy particularly for those with cardiac complications.

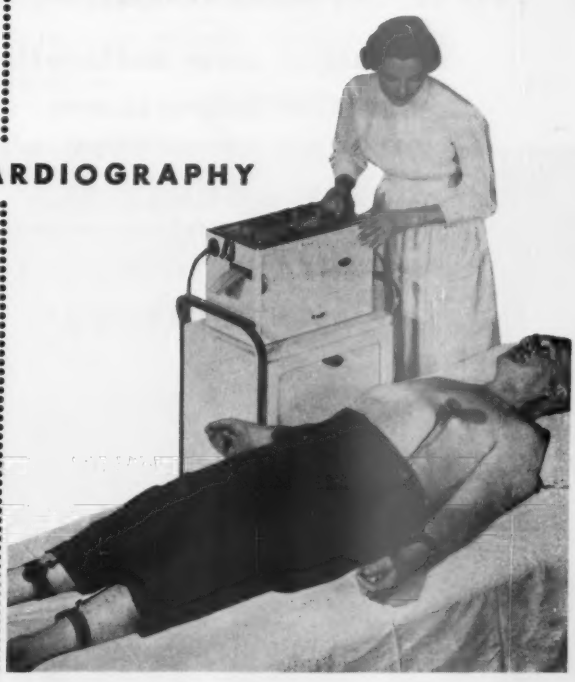
Supplied: White, 5 mg. oral tablets, bottles of 20 and 100. Pink, 1 mg. oral tablets, bottles of 100. Both are deep-scored.

*Schwartz, E.: New York J. Med. 56:570, 1956.

PFIZER LABORATORIES, Brooklyn 6, New York
Division, Chas. Pfizer & Co., Inc.

OFFICE ELECTROCARDIOGRAPHY

your patients are beginning to expect it.....



Just as the "health I.Q." of the general public has increased in recent years, so also has the awareness of diagnostic and therapeutic measures been broadened. The authoritative reassurance of a cardiogram recorded in your own office can be as helpful to your patients as the early diagnosis of heart disease can be to your own clinical management.

The BURDICK

ELECTROCARDIOGRAPH

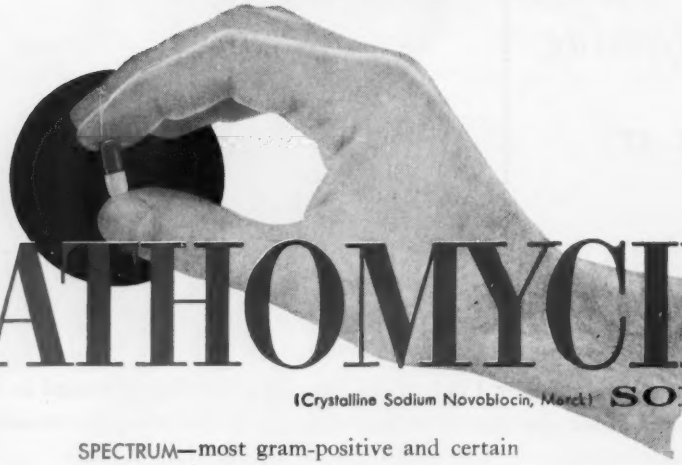
— provides time-saving features and precision engineering for accurate, dependable diagnostic service. Timing and leads are marked automatically, and leads can be switched rapidly without base line shift or distortion. Preset controls simplify operation.

See your Burdick dealer for demonstration.

THE BURDICK CORPORATION Burdick MILTON, WISCONSIN

NOW AVAILABLE...

a unique new antibiotic
of major importance
PROVED EFFECTIVE AGAINST
SPECIFIC ORGANISMS
(*staphylococci and proteus*)
RESISTANT TO ALL OTHER
ANTIMICROBIAL AGENTS



'CATHOMYCIN'

(Crystalline Sodium Novobiocin, Merck) **SODIUM**

SPECTRUM—most gram-positive and certain gram-negative pathogens.

ACTION—bactericidal in optimum concentration even to resistant strains.

TOXICITY—generally well tolerated. This is more fully discussed in the package insert.

ABSORPTION—oral administration produces high and easily-maintained blood levels.

INDICATIONS—cellulitis, pyogenic dermatoses, septicemia, bacteremia, pneumonia and enteritis due to *Staphylococcus* and infections involving certain strains of *Proteus vulgaris*, including strains resistant to all other antibiotics.

DOSAGE—four capsules (one gram) initially and then two capsules (500 mg.) twice daily.

SUPPLIED—Two capsules (500 mg.) twice daily or one capsule (250 mg.) four times a day.

'CATHOMYCIN' *is a trademark of Merck & Co., Inc.*

MSD

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC.
PHILADELPHIA 1, PA.

'Thorazine' relieved this patient's severe anxiety and fear. She was able to continue working and soon began to gain insight.

'THORAZINE' CASE REPORT

patient: 29-year-old single female. Severe anxiety of two months' duration. Complained to police of car following her home nightly. Afraid to quit job because of fear of reprisal by communists in her office.

response: Intensity of symptoms diminished rapidly when 'Thorazine' was given. After one week, "remarks were no longer directed at communists." Patient quit her job and got a new one.

After three months of 'Thorazine' therapy, patient stated that she "felt fine" and her "work was very good." "Maybe it was my nerves and imagination, but that's behind me."

This case report is from the files of the patient's physician.

THORAZINE* one of the fundamental drugs in medicine

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

to NORMALIZE, use KONSYL®

It is important, when inducing normal bowel function, to supply a non-irritating bulk to the colon, especially in those cases in which it has been necessary to eliminate from the diet the high roughage foods containing irritating bulk (lignin and cellulose).

It has been shown[1] that the colon resumes a more normal peristaltic pattern[2] when it is supplied with a stool of medium soft consistency of sufficient bulk[3], especially if the indigestible portion of that bulk consists primarily of hemicellulose.[4]

KONSYL is a vegetable concentrate of naturally occurring hemicelluloses. It is derived from blond psyllium seed and provides just the moist, smooth, effective bulk so essential to normal peristalsis. Its use has been shown to materially hasten the rate of improvement in patients with the irritable colon syndrome.[5] KONSYL contains 100% bulk producing material.

Furthermore, Konsyl is available in 6-ounce and 12-ounce containers at significantly lower-cost-to-patient prices. That's why we say

to NORMALIZE, use KONSYL®

1. Dolkhart, R. E., Dentler, M. & Barrow, L. L., Ill. M. J. 90:286, 1946.
2. Adler, H. F., Atkinson, A. J., & Ivy, A. C., Am. J. Digest. Dis., 8:197, 1941.
3. Wozasek, D., & Steigman, F., Am. J. Digest. Dis., 9:423, 1942.
4. Williams, R. D., & Olmsted, W. H., Ann. Int. Med., 10:717, 1936.
5. Lieberthal, M. M., Conn. State M. J., 19:86, 1955.

Formula: KONSYL contains 100% platago ovata coating.

Made by BURTON, PARSONS & COMPANY *Since 1932*

Originators of Fine Hydrophilic Colloids

WASHINGTON 9, D. C.

For Infectious Diarrhea

THE FULL ATTACK...

Antibacterial

Adsorptive

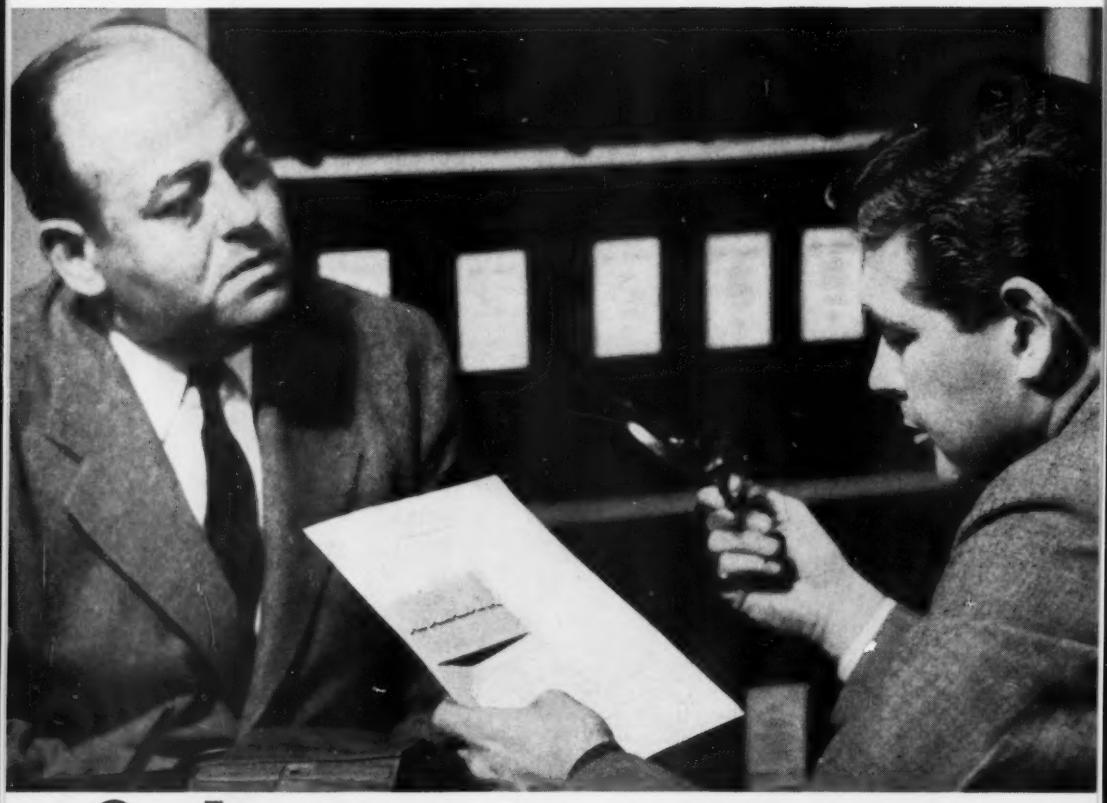
Protective

Streptomagma combats bacterial diarrhea with multiple forces. It offers dihydrostreptomycin to control the streptomycin-susceptible organisms. Simultaneously, its pectin, kaolin, and alumina gel soothe the irritated bowel, promote development of well-formed stools, and aid in the removal of bacterial toxins and irritants.

Wyeth®
Philadelphia 1, Pa.

STREPTOMAGMA®
Dihydrostreptomycin Sulfate and Pectin with Kaolin in Alumina Gel

to minimize straining at stool...



Colace softens stools for easy passage

DIOCTYL SODIUM SULFOSUCCINATE, MEAD JOHNSON*

without laxative action · without adding bulk

By its surface-active properties, Colace increases the wetting efficiency of intestinal water and promotes the formation of oil-water emulsions. Thus Colace keeps stools normally soft, and softens already hardened stools, for easy, natural passage.

Colace provides a new approach in the management of constipation. In patients with cardiac conditions, it prevents or greatly reduces straining at stool. Gentle and nonlaxative, Colace does not cause drastic emptying or overfrequent bowel movements. No undesirable side effects have been reported.

MEAD JOHNSON

SYMBOL OF SERVICE IN MEDICINE

SUGGESTED ORAL DAILY DOSAGE

Adults and older children	50 to 200 mg.
0 to 3 years	10 to 40 mg.
3 to 6 years	20 to 60 mg.
6 to 12 years	40 to 120 mg.

THE COLACE FAMILY

NEW Colace Capsules 100 mg., bottles of 30, 60 and 250.

Colace Capsules 50 mg., bottles of 30, 60 and 250.

Colace Liquid (1% solution; 10 mg. per cc.), 30 cc. bottles with calibrated dropper.

NOW Colace Syrup (an orange- and mint-flavored aqueous solution; 20 mg. per teaspoon), 8 ounce bottles.

*Patents pending

13687

In Urinary-Tract Infections

Preparation of Choice

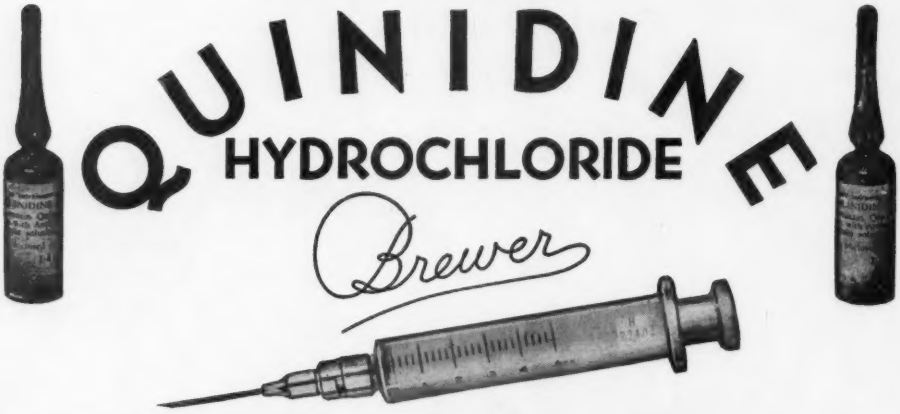
Wyeth®
Philadelphia 1, Pa.

SUSPENSION TABLETS

SULFOSE®

Triple Sulfonamides
(Sulfadiazine, Sulfamerazine, Sulfamethazine)

INJECTABLE QUINIDINE HYDROCHLORIDE



Brewer

FIRST *INJECTABLE QUINIDINE COMMERCIALLY AVAILABLE IN AMERICA*

TRIED - TESTED - DEPENDABLE - STABLE

For those cases of auricular fibrillation and paroxysmal tachycardia where QUINIDINE is indicated and cannot be given, or is not effective, orally—

Administration: **INTRAMUSCULARLY or if necessary INTRAVENOUSLY**

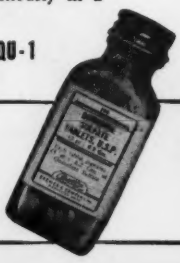
Available: **Quinidine Hydrochloride Injectable (0.6 Gm.) in 5 cc. ampul**

Quinidine Hydrochloride Injectable (0.18 Gm.) in 1½ cc. ampul

REFERENCES:

1. Sturnick, M. I.; Riseman, J. E. F.; and Sagall, E. I.: Studies on the Action of Quinidine in Man: J. A. M. A. 121; 917 (March 20) 1943
2. Sagall, E. I.; Horn, C. D.; and Riseman, J. E. F.: Studies on the Action of Quinidine in Man: Arch. Int. Med. 71; 460 (April) 1943
3. Armbrust, Chas. A. Jr. and Levine, Samuel A.: Paroxysmal Ventricular Tachycardia: A Study of 107 Cases: Circulation, 1; 28-39 (Jan.) 1950
4. Bell, G. O.; Bradley, R. B.; and Hurxthal, L. M.: Paroxysmal Tachycardia, Experiences with Massive Doses of Quinidine Intravenously in a Refractory Case: Circulation, 1: 939 (April Part II) 1950

For additional information — just send your ℞ blank marked 700-1



Also Available

FOR ORAL ADMINISTRATION

Quinidine Sulfate Tablets and Capsules (3 gr.) in bottles of 100, 500 & 1000.

BREWER & COMPANY, INC.

67 UNION STREET WORCESTER 8, MASS.

TECHNICAL EXHIBIT

of the

AMERICAN COLLEGE OF PHYSICIANS

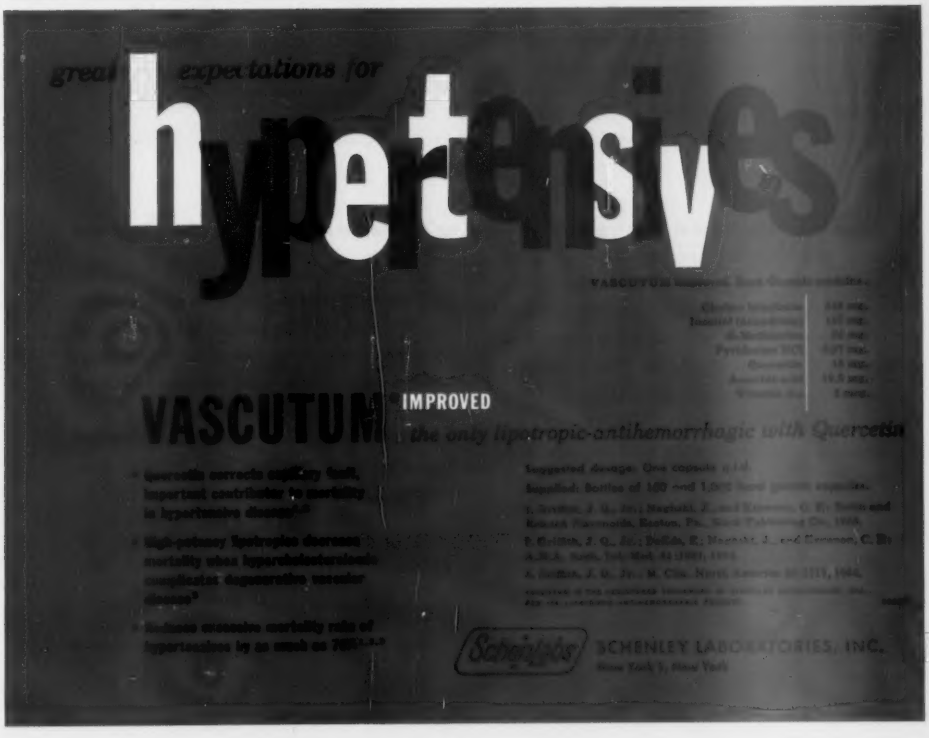
Boston, Mass., April 8-12, 1957

In connection with its 38th Annual Session, The American College of Physicians will conduct an excellent Technical Exhibit at the Mechanics' Building, Boston, the site of all scientific meetings except some of the panels and CPC's.

Exhibits will be restricted to products relevant to the practice of Internal Medicine or its allied specialties. Preference will be given to exhibits of a scientific nature, such as pharmaceuticals, equipment and medical books. All exhibits must be officially acceptable to the Committee on Advertisements and Technical Exhibits of the College.

One hundred or more select firms and organizations will present a galaxy of approved products of scientific interest. Members and guests of the College are encouraged to accord the exhibitors courteous and interested attention. Great expenditures are made by the exhibitors to bring to the College superior displays and up-to-date information concerning pharmaceuticals, equipment, medical publications and medical services.

Exhibit hours—8:45 A.M. to 5:30 P.M., Monday through Thursday; 8:45 A.M. to 2:15 P.M. Friday.



New...improved salicylate therapy

in a TANDEM RELEASE tablet

2-STAGE DISINTEGRATION . . .

The outer layer of Buffered Pabirin Tablets quickly releases aluminum hydroxide for buffering action. PABA to potentiate acetylsalicylic acid and therapeutic doses of ascorbic acid to offset depletion are also in the outer layer.

The inner core of Buffered Pabirin Tablets containing acetylsalicylic acid alone begins to expand after the buffering action has started.

Arthritic patients—the very patients who need salicylate therapy most—are also the ones least able to tolerate salicylates over prolonged periods without gastric distress. This problem is now solved by the new Buffered Pabirin Products. The protective antacid (aluminum hydroxide) buffers against gastric irritation. PABA and the antacid potentiate acetylsalicylic acid and rapidly create high, sustained blood levels with low salicylate dosage...higher than with PABA or buffers alone. Studies show that high salicylate plasma levels promote an increase in production of adrenal cortical hormones.

For resistant rheumatics, Buffered Pabirin AC Tablets provide the added benefits of hydrocortisone. The use of hydrocortisone with acetylsalicylic acid reduces corticoid dosage to minimize the danger of adrenal atrophy. And PABA retards breakdown of hydrocortisone by the liver thereby prolonging its effect.

Buffered Pabirin and Buffered Pabirin AC Tablets are both sodium and potassium free.

SMITH-DORSEY • Lincoln, Nebraska • a division of The Wander Company

☆ buffered for superior gastric tolerance

☆ buffered for faster pain relief

The inner core then disintegrates rapidly and permits fast absorption of the acetyl salicylic acid.

Buffered Pabirin AC Tablets release, in addition, hydrocortisone from the core.

RESULT:

- **increased range of motion**
- **faster pain relief**
- **superior gastric tolerance**

for most rheumatoid arthritics

Buffered Pabirin® TABLETS

300 mg.	Acetylsalicylic acid (5 gr.)
300 mg.	Para-aminobenzoic acid (5 gr.)
50 mg.	Ascorbic acid
100 mg.	Dried aluminum hydroxide gel

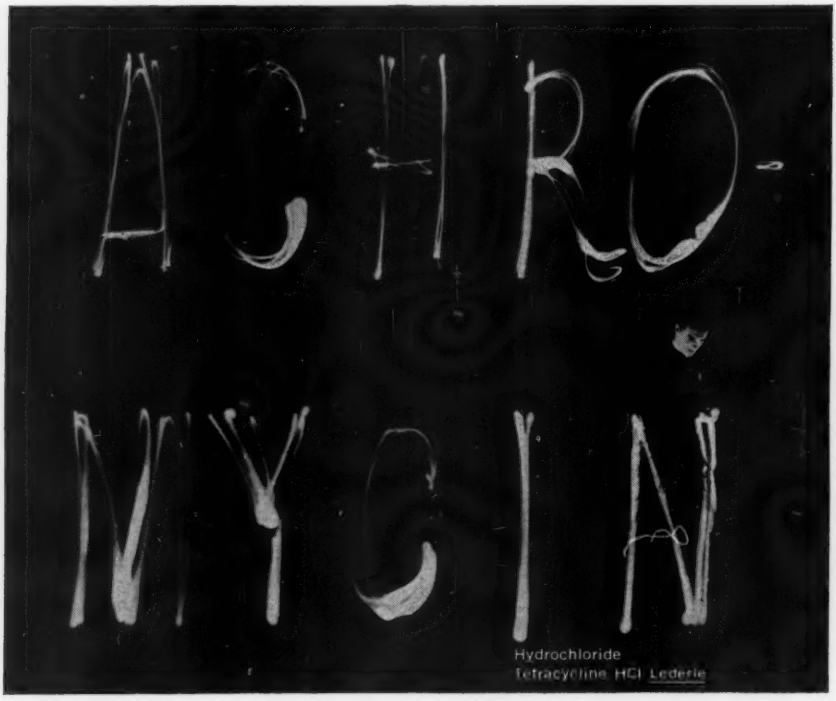
Dosage: Two or three tablets 3 or 4 times daily. In rheumatic fever three to five tablets 4 or 5 times daily.

for resistant rheumatics

Buffered Pabirin®AC TABLETS

2.5 mg.	Hydrocortisone
300 mg.	Acetylsalicylic acid (5 gr.)
300 mg.	Para-aminobenzoic acid (5 gr.)
50 mg.	Ascorbic acid
100 mg.	Dried aluminum hydroxide gel

Dosage: Initially, one or two tablets 4 times daily, after meals and on retiring. Reduction of dosage should be gradual; never stopped abruptly.



Liquid Pediatric Drops

aqueous suspension

stabilized, soluble, no oil to block absorption, no oily taste or repeat, remarkably free of side effects

ready-to-use, no refrigeration

freely miscible in water, milk, formula, or drop directly on tongue

handy, plastic dropper bottle

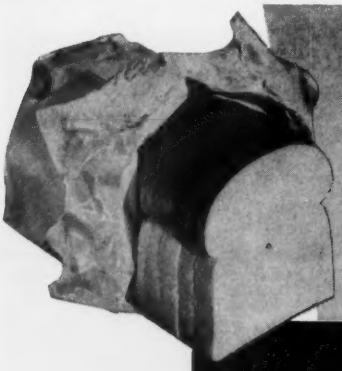
accurate dosage is easy, one drop per pound body weight per day

Supplied: 10 cc. plastic dropper-type bottle (cherry-flavor), 100 mg./cc. (approx. 5 mg. per drop)

ACHROMYCIN* Tetracycline ranks among the foremost in its field today... judged on its exceptional effectiveness against a wide range of pathogens, prompt control of infections commonly seen in medical practice, low incidence of side reactions. These outstanding features have been repeatedly confirmed by physicians everywhere during more than three years of clinical usage.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, N. Y.
*Reg. U. S. Pat. Off.

ACHROMYCIN...ACKNOWLEDGED FOR COMPETENCE



The Well-Proportioned Nutrients in Enriched Bread

Equally Important in Diets Moderately Low in Fat

The added nutrients in Enriched Bread are chosen qualitatively and quantitatively because of their importance in everyday nutrition. They have proved equally advantageous when dietary adjustment is indicated for therapeutic purposes.

In low-fat diets prescribed for many patients with coronary arteriosclerosis, gallbladder disease, hyperlipemia, obesity, and allied conditions, the proportions of the nutrients in enriched bread are especially significant.

The fat content of enriched bread approximates only 3 per cent, and its cholesterol content is negligible. This feature and, in addition, its well-balanced proportions of essential nutrients qualify enriched bread as an important constituent of low-fat diets.

Six slices of the average enriched bread, containing 4 per cent added nonfat dry milk, provide 12 grams of good quality protein (flour protein supplemented with milk protein), 0.36 mg. of thiamine, 0.26 mg. of riboflavin, 3.35 mg. of niacin, 3.5 mg. of iron, and 126 mg. of calcium—from 16 to 29 per cent of the adult patient's daily needs for each of these nutrients. Yet six slices of enriched bread supply only 19 per cent of the nutrient energy of a 2,000-calorie diet.

AMERICAN BAKERS ASSOCIATION
20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

Medihaler

Means self-powered, uniform, measured-dose inhalation therapy . . . made possible by specially designed metered-dose valve . . .

Medihaler

Means notably safe and effective therapy when indicated for children. Medication is in leak-proof plastic coated bottles . . .

Medihaler

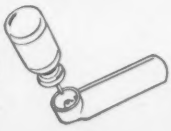
Means true nebulization. Each measured dose provides 80 per cent of its particles in the optimal size range—0.5 to 4 microns radius—insuring effective penetration of the respiratory tract.

Medihaler

Medication and Adapter fit into neat plastic case, convenient for pocket or purse . . .

Medihaler

Means an unbreakable Oral Adapter—no movable parts—no glass to break—no rubber to deteriorate . . .



Medihaler

Means greater economy—no costly glass nebulizers to replace, and one or two inhalations usually suffices for prompt relief.

Medihaler®

The Unique Measured-Dose Inhalation Method

In Asthma

For Rapid Relief of Acute or Continuing Bronchospasm

Medihaler-Epi™

Riker brand of epinephrine 0.5% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.125 mg. epinephrine. In 10 cc. vial with metered-dose valve, sufficient for 200 inhalations.

Medihaler-Epi replaces injected epinephrine in emergency situations in which respirations have not ceased. It provides rapid relief in acute food, drug, or pollen reactions (including urticaria, bronchospasm, angioneurotic edema, edema of glottis, etc.). In most instances only one inhalation is necessary.

Medihaler-Iso™

Riker brand of isoproterenol HCl 0.25% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.06 mg. isoproterenol. In 10 cc. vial with metered-dose valve, sufficient for 200 inhalations.

Note: First prescription for Medihaler medications should include the desired medication *and* Medihaler Oral Adapter.

℞ Medihaler-Iso and Medihaler Oral Adapter

Riker

ON THE FOLLOWING FIVE PAGES

MERCK SHARP & DOHME

ANNOUNCES...

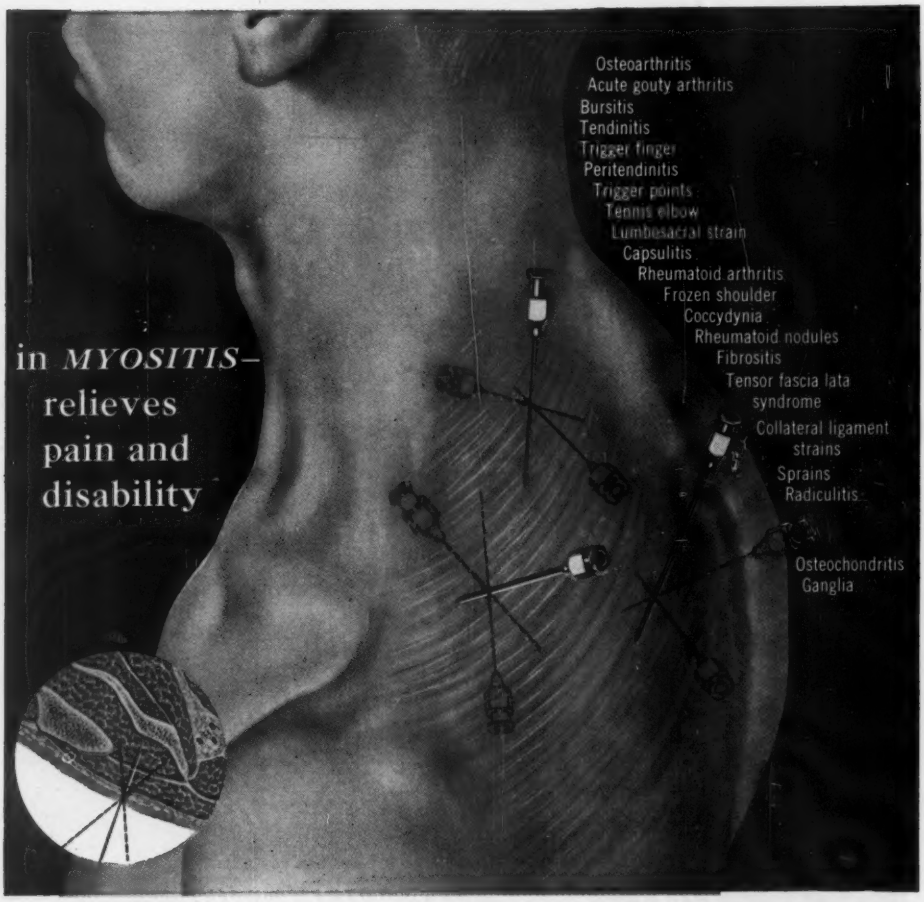
the most
effective,
longest lasting
adrenocortical steroid
yet developed
for
SOFT TISSUE,
intra-articular, and
intra-bursal injection

NEW

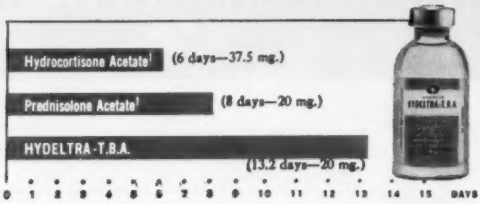
HYDELTRA® -T.B.A.

(Prednisolone tertiary-butylacetate, Merck)

for relief that lasts—longer



Anti-inflammatory effect lasts longer than that provided by any other steroid ester


Hydrocortisone Acetate[1] (6 days—37.5 mg.)
Prednisolone Acetate[1] (8 days—20 mg.)
HYDELTRA-T.B.A. (13.2 days—20 mg.)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 DAYS

Dosage: the usual intra-articular, intra-bursal or soft tissue dose ranges from 20 to 30 mg. depending on location and extent of pathology.

Supplied: Suspension 'HYDELTRA'-T.B.A.—20 mg./cc. of prednisolone *tertiary*-butylacetate, in 5-cc. vials.

MERCK SHARP & DOHME
DIVISION OF MERCK & CO., INC.
PHILADELPHIA 1, PA.

1. Hollander, J. L., *Paper read at conference in New York City, May 31 and June 1, 1955*

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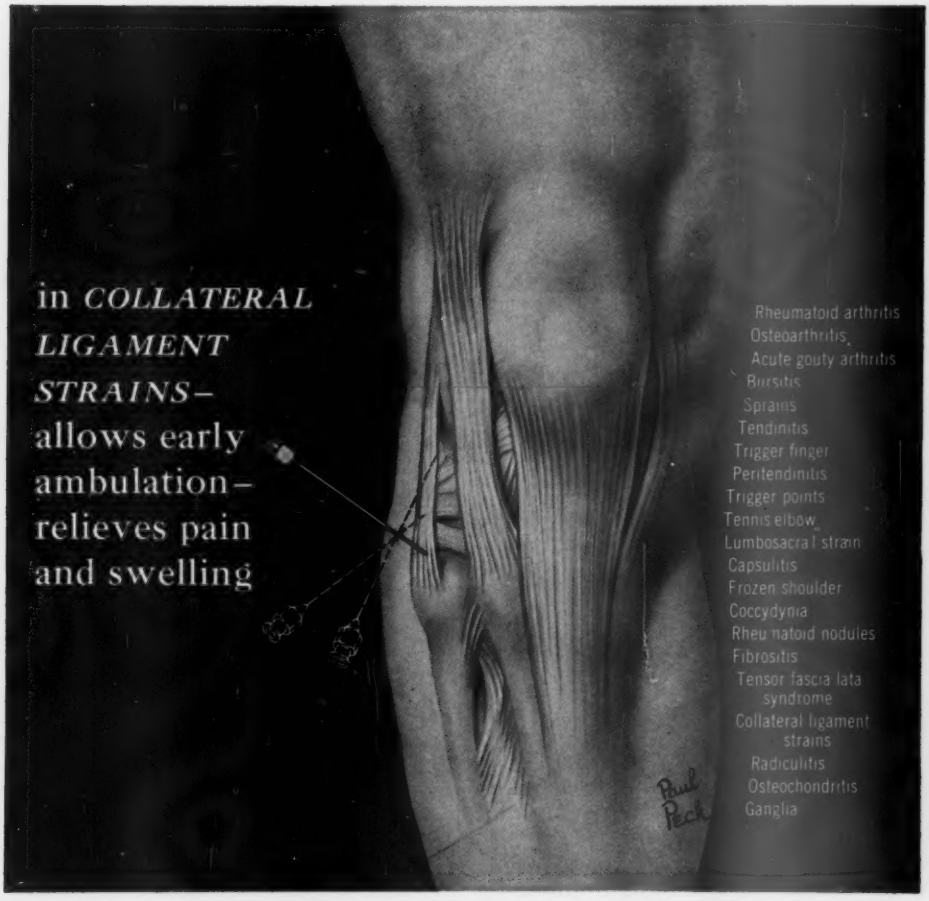
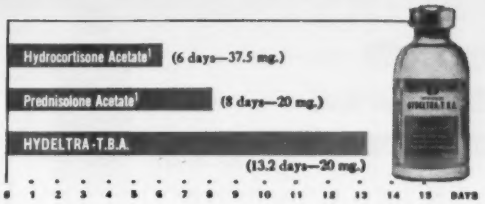


Duration of relief exceeds that provided by any other steroid ester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HYDELTRA® -T.B.A.

(Prednisolone *tertiary*-butylacetate, Merck)

for relief that lasts—longer

in *TENOSYNOVITIS*— often frees "locked" tendons without need for surgery

Osteoarthritis
Rheumatoid arthritis
Acute gouty arthritis
Bursitis
Tendinitis
Trigger finger
Tenosynovitis
Trigger points
Tennis elbow
Lumbosacral strain
Capsulitis
Frozen shoulder
Coccydynia
Rheumatoid nodules
Fibrositis
Tensor fascia lata syndrome
Collateral ligament strains
Sprains
Radiculitis
Osteochondritis
Ganglia

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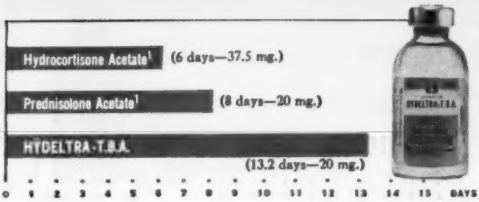
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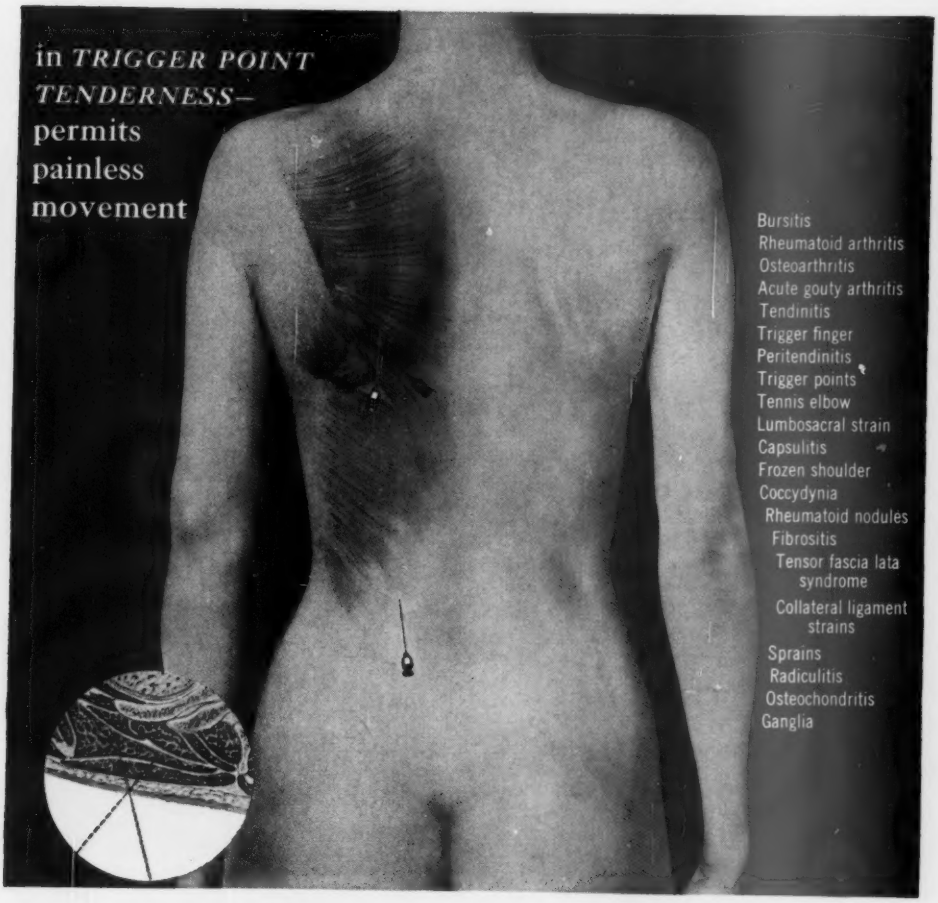

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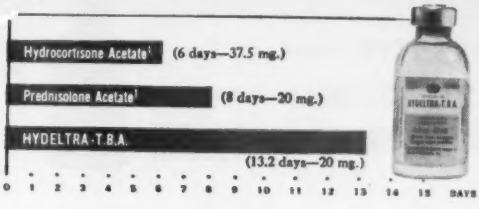
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for relief that lasts—longer

in *SPRAINS*—
reduces tenderness,
swelling and
limitation of motion

Osteoarthritis
Acute gouty arthritis
Bursitis
Tendinitis
Trigger finger
Peritendinitis
Trigger points
Tennis elbow
Lumbosacral strain
Capsulitis
Rheumatoid arthritis
Frozen shoulder
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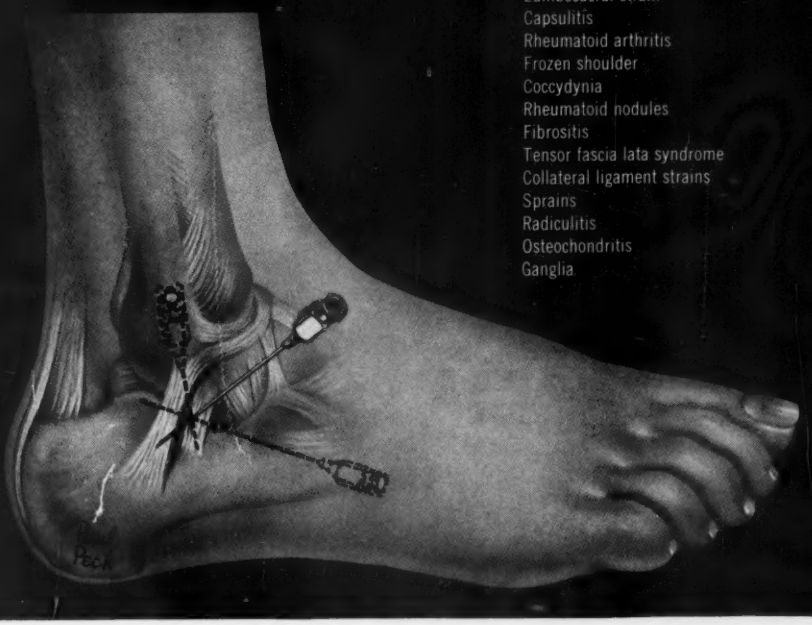
Radiculitis
Osteochondritis
Ganglia



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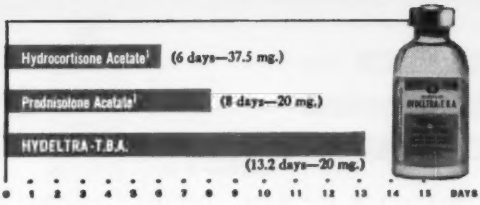
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1. Hollander, J. L., *Paper read at conference in New York City, May 31 and June 1, 1955*

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PATHOLOGIC PHYSIOLOGY OF THE BLOOD DYSCRASIAS: Washington University School of Medicine, St. Louis, Mo.; Carl V. Moore, M.D., F.A.C.P., William J. Harrington, M.D., (Associate), and Edward H. Reinhard, M.D., (Associate), Co-directors.			X							A. C. P. Annual Session, Boston, Mass.								A.M.A. Annual Meeting, New York City			
INTERNAL MEDICINE: The University of Chicago, The School of Medicine, Chicago, Ill.; Wright R. Adams, M.D., F.A.C.P., and Robert G. Page, M.D., Co-directors.															X						
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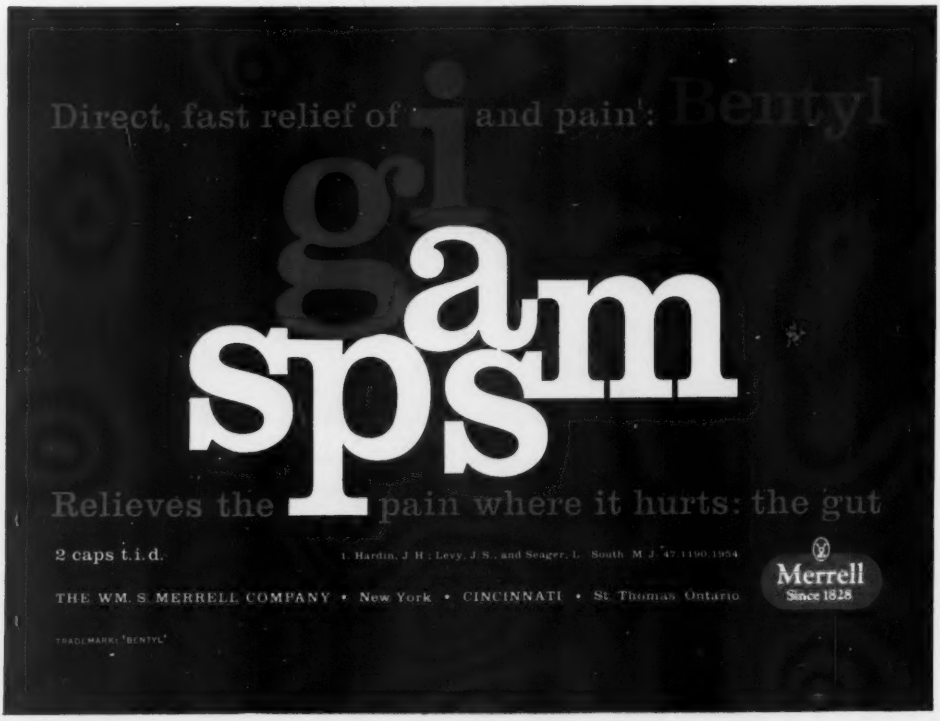
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ANNALS OF
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VOLUME 46 JANUARY, 1957 NUMBER 1

PROBLEMS IN THE MANAGEMENT OF ULCERATIVE COLITIS, WITH PARTICULAR REFERENCE TO ACTH AND THE ADRENAL STEROIDS *

By MANUEL SKLAR, M.D.† JOSEPH B. KIRSNER, M.D., F.A.C.P., and WALTER L. PALMER, M.D., F.A.C.P., *Chicago, Illinois*

INTRODUCTION

ULCERATIVE colitis is a serious disabling disease of variable course, with remissions and exacerbations at unpredictable intervals. Prior to adrenal corticotherapy, conventional medical management, although helpful in the majority of the patients, seldom produced dramatic results. In a series [1] of 100 cases reported in 1948, 53 patients were estimated to have benefited from medical therapy. Fourteen patients died; the most common cause of death (nine patients) was peritonitis secondary to perforation of the bowel. In a recent survey [2] of 180 cases treated with ACTH, cortisone, hydrocortisone and related compounds in the years 1950 through 1955, a satisfactory, often very dramatic response was observed in 85% of patients. Only six of the 12 deaths occurring among this group could be related in any way to hypercorticism; only one had peritonitis secondary to perforation of the colon, a complication probably antedating hormonal therapy. Although the recurrence rate among this group of patients, most of whom had severe and prolonged disease not responding well or consistently to conventional treatment, was 70%, ACTH and the corticosteroids appeared to be extremely useful and relatively safe adjuncts to the usual medical program.

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The following six cases describe in more detail the beneficial and the adverse effects of corticotherapy.

Case Reports

Case 1. Chronic ulcerative colitis with excellent response to ACTH, complicated by hypertension and acne.

A 31 year old white female was admitted December 28, 1955, with a four year history of chronic, nonbloody diarrhea. Medical treatment elsewhere had included azulfidine, without improvement. Two years earlier, symptoms had remitted during a pregnancy; however, the diarrhea increased in severity during the postpartum

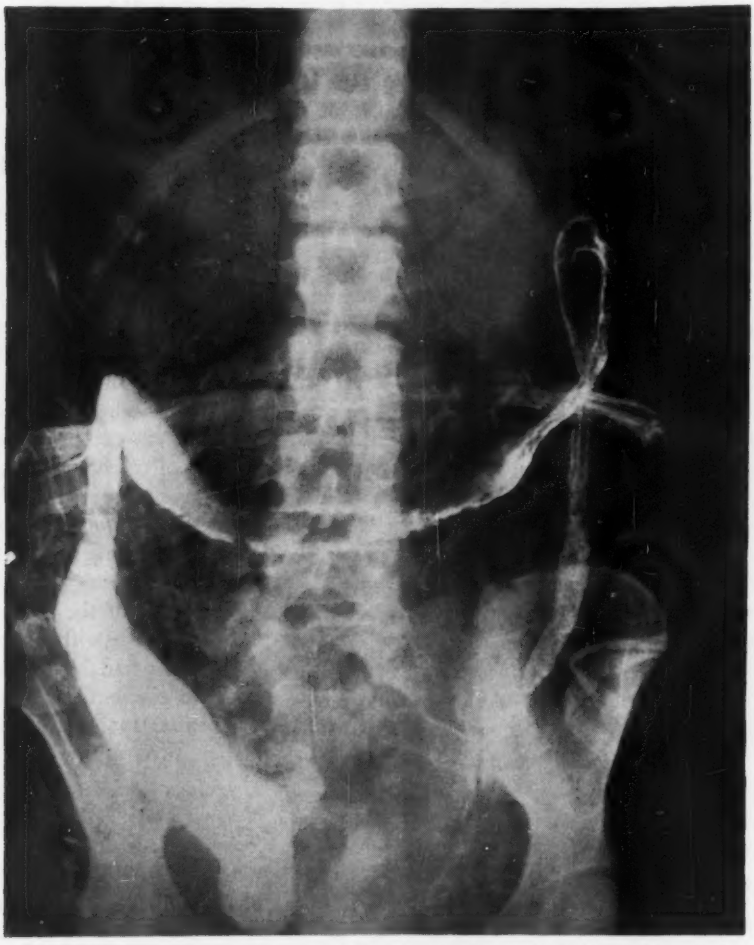

Fig. 1. *Case 1.* Barium enema, showing loss of haustrations, shortening and narrowing of the entire colon. An artifact consisting of a cloth waistband is seen.

period. At the time of admission the patient was passing eight to 10 nonbloody stools daily. Physical examination revealed a chronically ill woman; the blood pressure was 100/80 mm. of Hg; pulse rate, 120; respirations, 20; temperature, 37° C. There was moderate, generalized abdominal tenderness. Proctoscopy revealed granularity and moderate friability, changes characteristic of moderately severe active ulcerative colitis. The hemoglobin was 10.6 gm.%; red blood count, 3,470,000 cells per cubic millimeter; white count, 7,900, with a normal differential. The serum electrolytes were normal; the A/G ratio was reversed. Bacteriologic studies of the stools revealed no pathogens; occult blood was present. Barium enema disclosed loss of haustrations and shortening and narrowing of the entire colon (figure 1).

Treatment initially included a strict low-residue, nonlaxative diet, phenobarbital and belladonna, and sulfaguanidine. ACTH therapy, 120 units intramuscularly daily, was instituted on the fourth hospital day. Within one week the bowel movements had decreased to two semi-formed stools daily (figure 2). The patient experienced a marked sense of well being, and her appetite improved so that she consumed more than 3,000 calories per day. On the tenth hospital day she developed severe throbbing headaches; her blood pressure was recorded as 160/110 mm. of Hg. The dose of ACTH was halved, with relief of headache and return of blood pressure to normal, and without recurrence of bowel symptoms. Severe acne developed during the third week of hospitalization but responded to ultraviolet therapy and large doses of vitamin A. The patient continued to improve. On the fifty-seventh hospital day the medication was changed to ACTH gel, 40 units daily. She was discharged on the sixtieth hospital day with normal bowel function and a nearly normal appearing rectal mucosa on proctoscopic examination.

The dose of ACTH gel was decreased gradually to a daily dose of 20 units. The diarrhea recurred but subsided after an increase of the ACTH gel to 40 units per day. Subsequently, the dose has been decreased gradually, and for the last six months has been maintained at 20 units daily. The remission has continued in spite of a complete hysterectomy performed one month ago (figure 2).

Comment: This young woman with chronic active ulcerative colitis had received excellent conventional medical treatment elsewhere, without improvement. She responded strikingly well to ACTH, although two complications were encountered: hypertension, which disappeared when the dose of ACTH was decreased, and severe facial acne, which responded in part, at least, to dermatologic therapy. The symptoms recurred when the dose of ACTH gel was decreased to 20 units daily, a level apparently below the threshold required for control of the disease at that time. Subsequently, the patient has remained well on this same dosage, suggesting that the activity of the disease now has decreased. The normal appearance of the rectal mucosa on proctoscopic examination and the currently normal bowel function are further evidence of the favorable response to corticotropin.

Case 2. Fulminant ulcerative colitis responding to ACTH and prednisolone, complicated by psychosis and hypokalemic alkalosis.

A 22 year old white female was admitted on the night of June 4, 1955, with a history of sudden onset of diarrhea three weeks earlier; eventually becoming bloody in character, extreme urgency to defecate and abdominal cramps. Two days prior to admission she became febrile, weak and dehydrated; she failed to improve on intravenous fluids and blood transfusions. Physical examination revealed a dehydrated, acutely ill girl, with a pulse rate of 140, respirations of 28, and temperature

of 40° C. The abdomen was diffusely tender but soft, and the bowel sounds were active. Proctoscopy revealed edema, hyperemia and marked friability in the bowel, changes characteristic of severe active ulcerative colitis. The hemoglobin was 10.7 gm.%; hematocrit, 36%; white blood count, 10,200 cells per cu. mm. with a normal differential. The urinalysis was normal. The serum electrolytes were normal. Blood culture revealed no growth. The grossly bloody stools contained no ova or parasites; *Escherichia coli* was grown in culture.

A program of transfusions, intravenous fluids, ACTH intravenously (50 units/24 hours), penicillin, streptomycin, morphine and atropine was initiated, with dramatic response (figure 3). Within 36 hours the patient had become afebrile and the

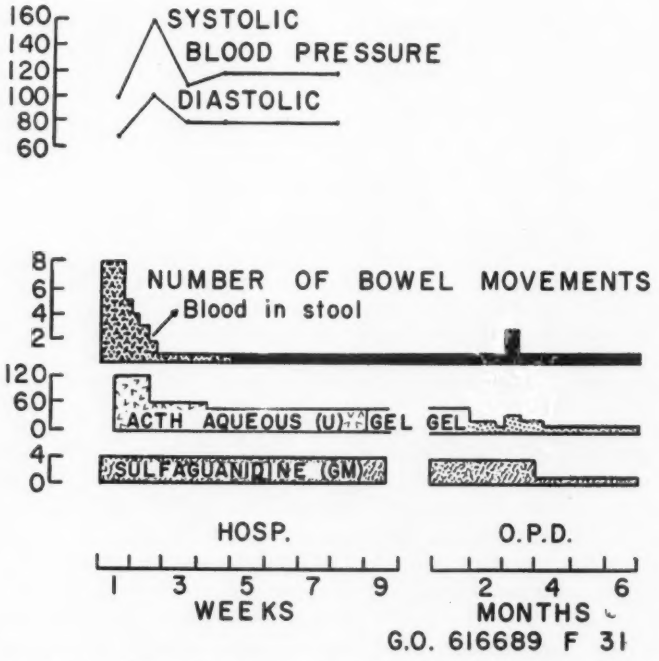

FIG. 2. *Case 1.* Illustration of favorable response to ACTH in a patient with severe chronic ulcerative colitis who had failed to respond previously to conventional medical therapy. Remission persists on ACTH 18 months following hospitalization.

diarrhea had decreased from innumerable stools to four liquid ones daily. On the seventh hospital day aqueous ACTH in a dose of 120 units intramuscularly daily was begun, together with a bland diet and sulfaguanidine. The opiates were withdrawn. On the twelfth hospital day the patient became somewhat confused and agitated; a low grade fever was noted, and the number of bowel movements increased from two to seven per day. The serum sodium and potassium were normal, but the carbon dioxide combining power had risen to 33.1 mEq. and the chlorides had fallen to 90.6 mEq. The dose of ACTH was increased to 150 units; chlorpromazine was added; potassium chloride was administered intravenously. On the following day, hemolytic *Staphylococcus aureus* and *E. coli* were cultured from

the urine, and Gantrisin was administered. The fever gradually subsided during the next week; however, the alkalosis progressed and hypokalemia developed. On the twenty-eighth hospital day the serum potassium had fallen to 3.0 mEq. and the CO_2 had risen to 32.7 mEq. At this time the patient was delirious. The ACTH was withdrawn rapidly. Chlorpromazine was increased to 400 mg. per day, and potassium was given orally in the form of concentrated meat broth. The day following withdrawal of ACTH the patient became toxic once more; the fever rose to 39.4° C.; the number of stools increased. The abdomen was distended and tender,

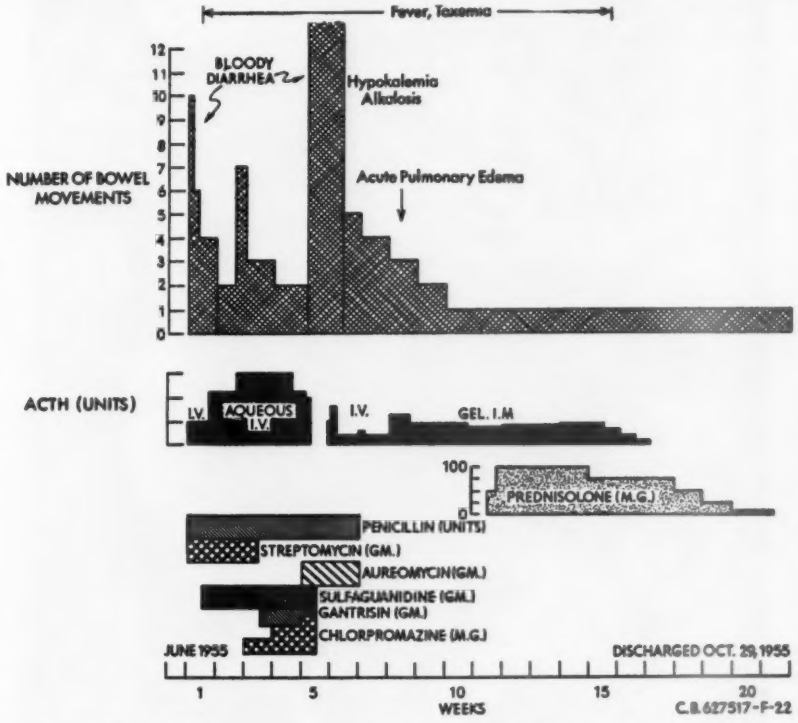

FIG. 3. *Case 2.* Diagrammatic representation of clinical course of patient, with fulminating colitis responding to ACTH and prednisone, but complicated by hypokalemic alkalosis, acute pulmonary edema and psychosis.

but bowel sounds were audible. There was no free air in the peritoneal cavity, either by physical examination or by x-ray. Intravenous therapy was re-instituted, Achromycin was added, and large doses of sodium amytal were administered. Her condition remained precarious, becoming even more critical on the thirty-fourth hospital day when, while receiving blood transfusions, she developed acute pulmonary edema, which responded to Cedilanid, morphine and aminophylline. At this time the serum sodium was 148 mEq.; serum potassium, 3.3; serum chloride, 93.4; carbon dioxide, 36.6 mEq. The hemoglobin had fallen to 8.9 gm. and the white count to 3,100. On the thirty-sixth hospital day ACTH again was administered intravenously, 40 units daily, and blood transfusions were given slowly. There was

gradual improvement in mental, bowel and electrolyte status over the next two weeks, and by the fiftieth hospital day the patient again was receiving a diet, oral medication and ACTH intramuscularly. On the fifty-fourth hospital day the white count was 1,700 and all medications except the ACTH and phenobarbital were

FIG. 4. *Case 2.* Post-evacuation x-ray film demonstrating extensive involvement of the colon.

discontinued. Within 10 days the white count rose to 6,100. On the seventieth hospital day the temperature increased to 39.8° C. and the pulse rate to 120 without associated symptoms. Prednisolone was then added, attaining a dose of 80 mg. per day; ACTH was withdrawn slowly. The fever and tachycardia gradually subsided. During this time the patient was passing one semiformed stool daily. Her mental

status was clear and the serum electrolytes were normal. On the one hundred thirty-fourth hospital day a barium enema revealed ragged borders of the sigmoid, descending and left transverse colon (figure 4). The patient continued to progress favorably. Prednisolone was withdrawn gradually and she was discharged on the one hundred forty-seventh hospital day, having normal bowel function. A normal rectal mucosa was observed by proctoscopic examination. The patient continues well six months after discharge from the hospital on a program consisting of a bland diet and phenobarbital and belladonna.

Comment: The rôle of ACTH and the corticosteroids in the management of fulminant colitis is considered by some to be restricted to the preparation of patients for surgery.[3] This case illustrates the dramatic beneficial effects in fulminating ulcerative colitis with adrenal hormone therapy. There is little doubt in our minds that corticotherapy saved the colon and perhaps the life of this young woman.

Two serious undesirable effects related to the high blood steroid level developed: (a) hypochloremic, hypokalemic alkalosis, and (b) steroid psychosis. The electrolyte disturbance was very severe, requiring intensive repletion with potassium chloride intravenously in large quantities, reaching a total of 200 mEq. daily. As oral feedings became possible, potassium was given as a concentrated meat broth containing 8 mEq. per 4 c.c., although, on the whole, we prefer the intravenous route when potassium is required. Potassium chloride tablets were not employed because of their tendency to aggravate diarrhea. The initial manifestations of psychotic behavior were treated with chlorpromazine, a drug we have found useful in controlling the agitation and excitement induced by corticosteroids. However, when the psychosis increased in severity, withdrawal of ACTH became necessary. The persistence of the psychosis in spite of these measures may have been related to the potassium deficiency or to the toxic state of the patient. Mental symptoms did not recur upon re-institution of corticotherapy one week later. The prognosis seems excellent in view of the relatively brief history and the apparent recovery, although prolonged careful medical supervision is indicated.

Case 3. Massive hemorrhage with dramatic response to ACTH and hydrocortisone.

A 33 year old white male was admitted on April 1, 1954, with a history of arthritis involving both knees and ankles of 10 weeks' duration, diarrhea for five weeks, and gross blood in the stools for two weeks. He had been treated elsewhere with cortisone, 100 mg. daily, for several weeks, without improvement. Physical examination revealed an acutely ill male, with a pulse rate of 128; respirations, 20; temperature, 38.4° C. Proctoscopic examination demonstrated spontaneous bleeding, edema and marked friability, evidence of severe active ulcerative colitis. The hemoglobin was 13 gm.%; the erythrocyte count, 4.29 million cells per cubic millimeter; white count, 10,900 cells per cubic millimeter. The ratio of albumin to globulin was 2.9 gm. to 3.6. The serum electrolytes were normal. Bacteriologic studies of the feces were negative. The patient was placed on a strict low-residue, nonlaxative diet; phenobarbital and belladonna were added, and cortisone, 125 mg. daily, was continued. Because of his failure to improve, on the fifth hospital day

oral feeding and cortisone were discontinued; fluids were administered intravenously; penicillin and sulfaguanidine were given. On the twelfth hospital day the patient began to bleed severely from the rectum; 18 units of blood were necessary during the next 48 hours. ACTH, 120 units daily, was given intramuscularly. The response to ACTH was dramatic: within 36 to 48 hours the bleeding decreased markedly and the patient became afebrile (figure 5). However, he suddenly developed acute pulmonary edema, probably related to hypervolemia. This responded

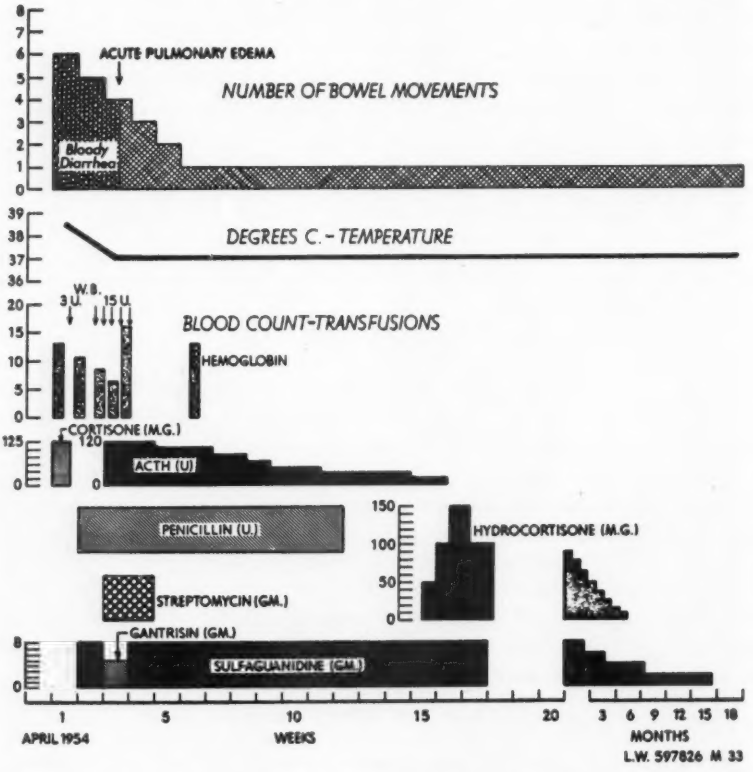

FIG. 5. *Case 3.* Dramatic cessation of rectal bleeding upon institution of ACTH therapy, with fulminant colitis characterized by hemorrhage.

to the usual measures, consisting of rapid digitalization and sedation with opiates. Except for a mild hypokalemic hypochloremic alkalosis and a brief psychosis manifested by depression, the patient made a gradual, uninterrupted recovery and was discharged on the one hundred twenty-first hospital day with normal bowel function and a virtually normal appearance of the bowel wall proctoscopically. During the final two weeks of hospitalization, hydrocortisone was added and corticotropin withdrawn gradually. The patient was continued on hydrocortisone therapy until February, 1955. He had received a total of 6,180 units of ACTH over a 92 day period, followed by hydrocortisone, 9.3 gm. over a period of 198 days. His clinical

condition remains excellent; he is having normal bowel movements, and the rectum appears practically normal at proctoscopy.

Comment: Severe hemorrhage is a serious complication of ulcerative colitis. In our experience, ACTH has been extremely useful in its control, as illustrated by this case. The relationship of the bleeding to previous cortisone therapy is questionable, since we have not observed an increased incidence of severe hemorrhage during or shortly after prolonged corticosteroid therapy. Bleeding probably is a primary manifestation of the disease, unrelated to steroids.

While ACTH is a more reliable agent for the immediate control of symptoms, oral steroids may be substituted for long-term maintenance therapy, once clinical control is established. The employment of corticosteroids for prolonged treatment has been an effective and convenient mode of therapy, and we have not observed serious adverse effects in patients so treated; the problem of adrenal insufficiency secondary to stress during or after steroid therapy has not been encountered. This man, observed for 22 months since discharge from the hospital and 14 months since the discontinuance of steroid therapy, has been leading a virtually normal life and, though he is yet vulnerable, his prognosis seems excellent.

Case 4. Severe ulcerative colitis with decreasing response to ACTH and hydrocortisone.

A 28 year old roller-skating instructor was admitted August 28, 1953, with a history of diarrhea and abdominal cramps of three months' duration. The symptoms had subsided after one month and the patient had been well for about six weeks, at which time the diarrhea recurred. Physical examination revealed no acute distress and no physical abnormalities. The blood pressure was 120/75 mm. of Hg; pulse rate, 84; respirations, 20; temperature, 37.5° C. Proctoscopic examination demonstrated edema, granularity and moderate friability, changes compatible with moderately severe active colitis. The hemoglobin was 14.8 gm.%; red blood cell count, 5.43 million per cu. mm., white blood cell count, 11,950 per cu. mm., with a normal differential count. The serum electrolytes were normal; the ratio of albumin to globulin was 3.5 gm. to 4.3. The stools contained occult blood. X-rays revealed the descending colon to be devoid of haustral markings.

Treatment with a low-residue, nonlaxative diet, sulfaguanidine, phenobarbital and belladonna was instituted. No improvement was observed, and on the seventh hospital day aqueous corticotropin therapy in a daily dose of 120 units was initiated. The bowel movements decreased by the third week to one or two daily, semi-formed, with no occult blood. Rounding of the face and acne had become noticeable. The ACTH was gradually decreased and finally discontinued on the fifty-first hospital day. Proctoscopic examination at this time revealed only granularity of the mucosa. Bowel function was virtually normal.

The patient returned to work and, except for brief, mild episodes of diarrhea, remained well until June, 1954, when he developed bloody diarrhea and was hospitalized the following month. Physical examination and laboratory studies were entirely normal. Gross blood was present in the feces. Proctoscopy revealed marked friability and spontaneous bleeding, indicating severe ulcerative colitis. In addition to the usual medical measures, therapy included corticotropin gel, 90 units daily. He responded well clinically, with gradual decrease in diarrhea and disappearance

of blood from the stool. Proctoscopically, however, little improvement was noted; the dose of gel was increased progressively, attaining a maximum of 180 units but without demonstrable benefit. Because of the patient's insistence for discharge, gel therapy was replaced after 70 days by oral hydrocortisone, 200 mg. daily. He was discharged October 9, 1954, but within one month was re-admitted because of a severe exacerbation of bloody diarrhea. Physical examination and laboratory studies again were not remarkable. The proctoscopic picture remained that of severe active colitis. Corticotropin gel was re-instituted, in a dose of 120 units daily, finally reaching 200 units, without visible change of the rectal mucosa and with only partial relief of symptoms. Intravenous ACTH therapy was employed for a week, without significant improvement. In spite of the intensive corticotherapy the serum electrolytes remained normal; acne and rounding of the face were prominent side effects. The eosinophil count throughout this period ranged from 40 to 60 per cu. mm., as compared to control levels of 150 to 250. Corticotropin therapy was discontinued on the thirty-seventh hospital day, and hydrocortisone, 200 mg. daily, was instituted. Symptoms gradually improved over the next two months; the dose of hydrocortisone was decreased gradually to 160 mg., and the patient was finally discharged on the one hundred twentieth hospital day, February 18, 1955. He was passing three to five loose, often bloody, bowel movements daily. The proctoscopic appearance of the bowel was unchanged. The symptoms gradually increased and he was again hospitalized on April 27, 1955. Physical examination now revealed an acutely ill man who nevertheless appeared well nourished. The blood pressure was 130/80 mm. of Hg; pulse rate, 108; respirations, 30; temperature, 38.6° C. The abdomen was tender, without rigidity. The hemoglobin was 11.0 gm. and the white blood cell count, 12,000. Serum electrolytes were normal. Corticotropin and hydrocortisone were administered intravenously, with decrease in the signs of toxicity but with little change in the frequency and consistency of the bowel movements. A subtotal colectomy and ileostomy was performed on May 5, 1955. The postoperative course was complicated by jaundice of unknown etiology, abdominal pain tentatively attributed to an intra-abdominal abscess, and splitting of the ileostomy stump during finger dilatation. None of these complications appeared attributable to the hypercorticoid state; there was no impairment of wound healing. An abdominal perineal resection was performed on June 6 and the ileostomy was revised. No abscess was found; the cause of the abdominal pain was not explained. The postoperative course was uneventful. The patient has made an excellent adjustment to his ileostomy and has been leading a virtually normal life.

Comment: This case represents a severe, progressive form of ulcerative colitis responding well, although not completely, to the first course of corticotropin therapy. The response to successive courses of both ACTH and hydrocortisone progressively diminished, until finally no significant beneficial effect could be elicited and surgery became necessary. While patients usually respond satisfactorily to repetitive courses of corticotherapy, the response to each succeeding course often is not so good as that observed during the previous course of treatment. This phenomenon of apparent increased resistance, also noted by others,[4, 5] may be related to progression in the severity of the disease or to the development of tissue refractoriness to corticosteroids. Perhaps inactivation of corticotropin occurs within the muscle or by means of circulating antihormones.

The danger of impaired wound healing following surgery has been considered a serious complication of corticotherapy.[6] We have occasionally

noted this problem in patients who were debilitated and malnourished as well as hypercorticoid at the time of operation. This patient, who had received large doses of ACTH and hydrocortisone for several months but who had been maintained in a good nutritional state, did not manifest any delay in the healing of his operative wound. The nutritional state at the time of surgery may be the crucial factor in determining whether satisfactory tissue repair will occur.[7]

Case 5. Atypical ulcerative colitis responding slowly to hydrocortisone and ACTH, complicated by septicemia, lung abscess and psychosis.

A 16 year old boy was admitted on December 22, 1954, with a history of red blood in the feces, first noted 18 months previously. Shortly thereafter he developed abdominal cramping and diarrhea; his local physician performed a hemorrhoidectomy and prescribed paregoric, with partial relief of symptoms. Eight months prior to admission the symptoms recurred; treatment with diet, penicillin and corticotropin gel had not produced significant improvement. The diarrhea consisted of 10 to 25 bloody stools daily; a perineal pad was required for the constant discharge. At the time of admission he had lost 40 pounds in weight. Physical examination revealed an emaciated, acutely and chronically ill adolescent male. The blood pressure was 110/80 mm. of Hg; pulse, 100; respirations, 24; temperature, 39° C. There was moderate lower abdominal tenderness. Three draining perianal fistulae were noted. Proctoscopic examination disclosed sinus tracts in the rectum, but the mucosa appeared normal. The hemoglobin was 10.4 gm.%; red blood cell count, 4.22 million cells per cu. mm., white blood cell count, 16,300 cells per cu. mm. with a normal differential blood count. Serum electrolytes were as follows: sodium, 128 mEq.; potassium, 3.2; chlorides, 91.7; carbon dioxide combining power, 24.1 mEq. The A/G ratio was reversed, with 2.8 gm.% albumin and 3.2 gm.% globulin. The diagnosis was thought to be ulcerative colitis of the segmental type. A subsequent relapse, to be described, may be interpreted as verification of this diagnosis.

Treatment consisted of nothing by mouth, intravenous fluids containing appropriate electrolytes to correct the existing imbalance, penicillin, streptomycin, sedatives, and hydrocortisone intravenously. An indwelling intravenous polyethylene catheter was inserted. Frequent blood transfusions were given. Although a prompt defervescence occurred, the patient continued to have numerous bowel movements and to be incontinent. On the eighth hospital day corticotropin, 30 units per 24 hours intravenously, was added to the program. The frequency of bowel movements diminished; however, on the twelfth day the temperature rose to 39.4° C., and blood culture revealed a pure growth of hemolytic *Staphylococcus aureus*, sensitive to tetracycline and erythromycin. The former antibiotic, because of its availability, was administered intravenously in a dose of 1.0 gm. daily. Steroid therapy was continued. Two days later the dressing over the site of insertion of the polyethylene catheter was changed and the area was discovered to be severely infected with the identical organism grown in the blood culture. Although no growth was obtained in the blood after the fourth day of tetracycline therapy, the patient once again became febrile and erythromycin was substituted in an intravenous dose of 600 mg. daily. The infected catheter was removed. The fever abated and erythromycin was continued for 17 days, with apparent clinical cure of the septicemia.

During this period of intensive antibiotic therapy, extending from the twelfth to the fortieth hospital day, intravenous hydrocortisone was gradually discontinued and intravenous corticotropin therapy maintained, with gradual improvement in the diarrhea. By the fortieth hospital day the stools had decreased to two per day, and had become semi-formed and free of occult blood. Intravenous therapy was

discontinued and the patient was placed on a strict low-residue, nonlaxative diet; ACTH was administered intramuscularly. At that time, however, the patient became extremely depressed and threatened suicide; he was considered to be in a state of steroid psychosis. He was transferred to the psychiatric ward and the corticotropin was gradually withdrawn. The depressed state gradually abated but during the eighth week of hospitalization a cough developed and the temperature rose to 38.4° C. Chest x-ray revealed a cavity 4 cm. in diameter in the right upper lobe. Hemolytic staphylococci were cultured from the sputum; erythromycin therapy was re-instituted. The temperature returned to normal, and serial x-rays of the chest demonstrated a gradual decrease in the size of the cavity, with virtual disappearance at the time of discharge on the one hundred second hospital day. X-rays of the colon and small bowel revealed no abnormalities in the colon, but several loops of distended jejunum and one loop with abnormal mucosal pattern suggested the diagnosis of regional enteritis. At the time of discharge the patient was having two semi-formed movements per day; his weight was 60.6 Kg., 17 Kg. greater than at the time of admission. Treatment included only a bland diet and 1.5 gm. of erythromycin daily. The latter drug was discontinued on June 6, 1955. The patient remained very well and returned to school in September, 1955. He then took a part-time job, began to stay out late at night and finally, in January, 1956, after suffering severe exposure to cold, once again developed diarrhea and fever. He was re-admitted to the hospital on February 7, 1956, with a temperature of 38.4° C. No physical abnormalities were detected. Proctoscopic examination revealed granularity and moderate friability of the rectal mucosa, confirming the original clinical impression of moderately severe active ulcerative colitis. The hemoglobin was 10.5 gm.%; white cell count, 11,500 per cubic millimeter, with a normal differential. The serum albumin was 3.4 gm.%, serum globulin, 3.1. The stools contained gross blood.

The patient was placed on a regimen consisting of strict diet, phenobarbital, belladonna and sulfaguanidine, 8.0 gm. per day, with no improvement. On the fourth hospital day corticotropin was begun, with gradual and sustained improvement; by the fourteenth day he was passing one to two semi-formed to formed bowel movements daily. He was discharged on maintenance corticotropin therapy on the thirtieth day, with no adverse effects to the present time.

Comment: Severe disseminated and often masked infection has been reported as a serious, though infrequent, complication of adrenal hormone administration.[8] Steroid therapy in this case was complicated by septicemia, in no way masked; the fever and clinical signs of toxicity were prominent. Although the high blood steroid level may have contributed to the dissemination of the staphylococci, the origin and immediate cause was an infected, indwelling intravenous catheter. A similar complication has been observed in other patients with indwelling intravenous catheters, not receiving steroids.

Appropriate antibiotic therapy successfully controlled this infection, though corticotherapy was maintained. The rationale for continuing treatment with the adrenal hormones was the danger of two serious complications which might have followed withdrawal: severe exacerbation of an improving ulcerative colitis, and adrenal cortical failure. An adequate adrenal response to the stress of severe infection could not be relied upon in a patient who had been receiving large doses of steroids for several days. The consequences of these probabilities seemed to outweigh the disadvantage

of impaired tissue response to infection associated with the hypercorticoid state. In our experience, it has usually been possible to manage successfully severe pyogenic infection by the addition of intensive antibiotic therapy without withdrawing the steroid.

An indication for withdrawal of hormonal therapy came when the psychosis, manifested by depression and suicidal tendencies, developed and constituted a serious threat to life; drug therapy could not be relied upon to control the psychiatric state. Since ulcerative colitis usually does not recur during psychotic episodes upon withdrawal of corticotropins, ACTH was discontinued without reluctance.

Despite the problems of steroid treatment in the initial hospitalization, re-institution of ACTH caused no such adverse effects during the second hospital admission. The patient was in a much better physical and mental condition. An excellent clinical response was obtained, and the patient remains well with maintenance corticotropin therapy.

Case 6. Peptic ulcer developing during course of hydrocortisone therapy.

A 21 year old white male was admitted June 26, 1954, with a history of fever, diarrhea, bloody rectal discharge, crampy abdominal pain and a 50 pound weight loss for one year. A right colectomy and a side-to-side ileo-transverse colostomy, performed elsewhere in April, 1948, for similar complaints, had established the diagnosis of ulcerative colitis. The patient had remained well until November, 1953, when he developed a febrile upper respiratory infection, followed by persistent diarrhea. A barium enema was said to have revealed recurrent ulcerative colitis, and a total colectomy was to have been recommended. Physical examination revealed a well developed young man in no distress. The blood pressure was 115/80 mm. of Hg; pulse, 72; respirations, 18; temperature, 37° C. No physical abnormalities were detected. Proctoscopy revealed a granular mucosa with scattered bleeding points and minimal friability, suggestive of mildly active chronic ulcerative colitis. The hemoglobin was 15.3 gm.%; red blood cell count, 5.14 million per cubic millimeter; white blood cell count, 9,350 per cubic millimeter, with a normal differential. Occult blood was present in the feces. X-ray examination of the colon disclosed extensive pseudopolyposis of the transverse colon and an irregular narrowing in the mid-descending colon (figure 6). Exfoliative cytologic study of material obtained from the colon was negative for malignant cells.

A regimen consisting of bland diet, Gantrisin, phenobarbital and belladonna was instituted, with little improvement. On the nineteenth hospital day, hydrocortisone, 200 mg. daily by mouth, was initiated. A prompt defervescence followed; the stools decreased in frequency and improved in consistency. Steroid therapy was discontinued on the fifty-third day and the patient was discharged on the sixty-first day with normal bowel function. Subsequently, he gradually lost weight and bowel activity increased. The temperature was 38° C.; physical examination otherwise was not remarkable. The proctoscopic appearance of the bowel resembled that originally seen. Laboratory studies revealed no abnormalities except for a low plasma iron level of 25 gamma %; occult blood again was detected in the stool. Roentgen examination of the colon revealed little significant change since the previous study. Hydrocortisone again was administered, with gradual though less striking improvement than had been observed during the first course of steroids. The hemoglobin decreased to 10.6 gm.; blood transfusions were administered. After two weeks of steroid therapy the patient noted postprandial epigastric distress. A gastroduodenal x-ray demonstrated a probable ulcer crater near the apex of the duodenal

bulb. Calcium carbonate and antisecretory drugs were added to the program, and hydrocortisone was continued. The epigastric distress disappeared and did not return; later x-rays revealed only deformity of the duodenal bulb; the crater was not definitely visualized. The patient was discharged on the sixtieth hospital day; his bowel function had returned to normal, but occult blood persisted in the stool. The recommendation for surgery, suggested because of the possibility of a bleeding neoplasm, was rejected by the patient. He has been maintained on hydrocortisone and antacid therapy during the past year; he has felt well and his bowel function has been essentially normal, yet occult blood persists in the stool and there has been a gradual loss of weight. His prognosis remains uncertain.

FIG. 6. *Case 6.* Barium enema, demonstrating pseudopolyposis of the transverse colon and irregular narrowing in the mid-descending colon; a right colectomy and side-to-side ileotransverse colostomy had been performed elsewhere in 1948.

Comment: This young man with moderately severe ulcerative colitis responded to hydrocortisone therapy, with virtually complete symptomatic control of the disease. The persistence of bleeding may indicate the presence of a complicating neoplasm which, of course, could not be influenced favorably by corticosteroids. The apparent development of a peptic ulcer during steroid therapy is unusual in our experience, for it is the only such instance in a series of 180 patients with ulcerative colitis treated with ACTH or steroids; 12 had a history of peptic ulcer or x-ray evidence of a deformed duodenal bulb prior to treatment with steroids and did not experience a recurrence. Hormone therapy was continued, and complete healing of the ulcer was achieved with antacid therapy. In our experience, the presence of a peptic ulcer or the history thereof is not a contraindication to the use of ACTH or corticosteroids, provided the indications for such therapy are acceptable. The present case indicates that the development of an ulcer during a successful course of corticotherapy does not necessitate discontinuance of steroids. Since the patient had not had gastrointestinal x-rays prior to treatment, the possibility of a preëxisting ulcer cannot be excluded.

Discussion

The value of ACTH and related drugs in the treatment of ulcerative colitis has received considerable re-affirmation in the recent literature. Truelove and Witts [9] reported a controlled study of 109 cases treated with cortisone and 101 cases managed without steroids. Remissions were significantly more frequent in the cortisone-treated group, and the course of those patients treated during the first episode of disease activity was particularly better than those untreated. Maltby and coworkers [10] also describe favorable results in 109 cases of ulcerative colitis treated with ACTH or cortisone.

That ACTH and the corticosteroids are capable of ameliorating the symptoms in the majority of cases of ulcerative colitis, at least initially, is established. The extent to which these compounds, when administered in conjunction with conventional medical management, may reverse the disease process and alter the natural history of the disease remains uncertain. Lives have been saved and operations at least delayed by their use. Admittedly, the period of steroid therapy (1950–1956) is relatively brief in comparison to the long duration of the ulcerative colitis in most patients. However, there is evidence, at least in patients treated early, that the course of the disease can be altered favorably.

These hormones thus appear worthy of trial in those cases of ulcerative colitis not responding quickly and completely to conservative medical measures; fulminant colitis is an indication for their immediate use, since surgery frequently can be avoided thereby.

The undesirable effects most commonly associated with corticotherapy include Cushing-like changes in appearance (rounding of face, acne, hirsutism, buffalo obesity and striae), edema, hypertension, hypokalemic

alkalosis, and disturbance in carbohydrate metabolism, manifested by glycosuria and hyperglycemia. However, these side effects rarely require withdrawal of the hormones.

The majority of patients treated with ACTH or corticosteroid in amounts required to control and then maintain improvement in ulcerative colitis will develop changes in facial appearance. These alterations usually are of little consequence; however, young women, and occasionally young men, may strongly object to the disfigurement, and decrease in dosage may become necessary. Edema and hypertension occur more frequently with ACTH and can be controlled by rigid restriction of salt intake, decrease in dose (as was illustrated in case 1) or by substituting hydrocortisone, prednisone or prednisolone. Mercurial diuretics and Diamox have been employed to control edema but, since these drugs also induce loss of potassium, they should be prescribed with great care.

ACTH, cortisone and hydrocortisone accelerate the excretion of potassium, and a hypokalemic, hypochloremic alkalosis may result.[11] While this electrolyte imbalance usually can be prevented by the prophylactic oral administration of potassium chloride, we avoid the oral use of potassium because of its tendency to aggravate the diarrhea in patients with ulcerative colitis. Frequent determinations of the serum potassium thus become mandatory; if the level falls significantly, repletion becomes necessary. Potassium chloride intravenously is the treatment of choice in the hospitalized patient. This route of administration is recommended only in patients with good renal function; the maximal rate of infusion should not exceed 20 mEq. per hour.[12] In the patient whose disease has stabilized, oral potassium salts may be risked, or the newer synthetic steroids, prednisone or prednisolone, may be substituted for ACTH.

Hyperglycemia and glycosuria, occurring in occasional nondiabetic patients during corticotherapy, usually are not troublesome problems; rarely is insulin necessary. Diabetics when treated with corticoids, however, commonly require an increase in insulin dosage. These alterations in carbohydrate metabolism are related to interference with the renal tubular re-absorption of glucose and to an increase in filtered load, the glucocorticoids promoting gluconeogenesis from protein and fat and depressing oxidation of glucose.[13] "Steroid" diabetes is characterized by insulin insensitivity, complete reversibility and little tendency toward ketosis;[14] potassium depletion may be a significant factor in the production of this syndrome.[15]

The problem of steroid-induced psychosis has been emphasized not because of its frequency but because of the potentially serious consequences, such as self-destruction. It is difficult to estimate the general incidence of psychosis in patients treated with adrenal hormones; however, Glaser[16] has suggested an over-all incidence of 5%, which agrees with our experience (10 of 180 patients). There is some question[17] as to whether the pre-

treatment psychic structure is related to the mental effects induced by these drugs, although the consensus is that such a relationship does exist.[13, 18] Furthermore, there is no clear correlation with daily dosage, total amount or duration of therapy;[19, 20] the majority of psychoses, however, seem to occur in patients receiving large daily doses of ACTH or corticosteroids.[18] The premonitory symptoms of an impending psychotic break include scalp paresthesias, restlessness, agitation, excitement, emotional lability, paranoid expressions, change of mood or suicidal thoughts. These symptoms necessitate a decrease in dosage of the adrenal hormone, the addition or increase of sedation, and perhaps the use of the newer tranquilizer drugs such as chlorpromazine. The development of an overt psychosis requires constant supervision of the patient by nurse or attendant, or transferral to a psychiatric ward; it constitutes an indication for discontinuation of hormonal therapy.

Disseminated infection occurring during corticotherapy is a somewhat less frequent but equally serious complication and is related to the ability of the glucocorticoids to suppress the inflammatory response and interfere with the capacity of the tissue to segregate and dispose of bacteria and toxins. Corticoid therapy should be continued, as illustrated in case 5; large quantities of appropriate antibiotics as determined by sensitivity studies are indicated. There is considerable experimental and clinical evidence suggesting that severe infection in hypercorticoid patients can be controlled by the administration of adequate amounts of one or more antibiotics to which the offending organism is sensitive.[21] A careful search for a focus of infection should be made.

The single instance of peptic ulcer during steroid therapy is recorded to emphasize our experience, as well as the experience of other investigators,[22] that the probability of such a complication seems to be no greater than the expected incidence of peptic ulcer in the general population.

Perforation of the colon, giant ulceration and massive hemorrhage have been attributed to sterogenic effect when occurring during the course of corticotherapy in patients with ulcerative colitis. In our experience, now approximating 200 patients, perforation has been observed in only two cases; in one instance the perforation was thought to have preceded corticotropin therapy. Truelove and Witts[9] reported two perforations, both in patients not receiving steroids. Giant ulceration and massive hemorrhages have been observed to respond favorably to corticoids. These complications thus seem to be related to the severity of the disease process rather than to the therapeutic agents employed.

Summary

Six cases of ulcerative colitis have been described, illustrating the rôle of ACTH and the corticosteroids in therapy. ACTH, aqueous, appears to be the hormone of choice; however, hydrocortisone and the newer

analogues often are successful when employed initially; and they are extremely valuable for prolonged maintenance therapy. They are also useful substitutes for ACTH when edema, hypertension or electrolyte disturbance develops after an initially satisfactory response to corticotropin. ACTH gel has not been so reliable as the aqueous preparation. Decreasing responsiveness to successive courses of corticotherapy has been noted. The optimal duration of steroid therapy in patients with ulcerative colitis is difficult to predict; continuous, prolonged therapy for months and years seems desirable in numerous cases.

The untoward effects associated with adrenal hormone administration include Cushing-like changes, edema, hypertension, hypokalemic alkalosis, psychosis and infection. The Cushing-like changes in appearance are of little significance and can be controlled at least partially by a decrease in dosage. Edema and hypertension may be troublesome; both may be minimized by drastic restriction of salt intake, decrease in dose of ACTH or substitution of prednisone or prednisolone. Because of the irritating effect of oral potassium salts on the gastrointestinal tract, hypokalemic alkalosis is a more common and therapeutically more complex problem in ulcerative colitis than in patients able to tolerate such salts. Intravenous potassium repletion is recommended in the hospitalized patient; oral potassium chloride may be risked in the ambulatory individual. The newer steroid analogues are less likely to produce electrolyte imbalance. Psychosis, while not common, is a serious complication of corticotherapy. Reduction in dosage and the use of sedatives, including the tranquilizing agents, are indicated at the earliest sign of disturbed behavior. A frank psychotic break necessitates withdrawal of hormone therapy. Fortunately, exacerbation of the colitis does not usually occur under these circumstances. Disseminated infection is the least common of the untoward effects mentioned. Intensive antibiotic therapy is indicated; the corticoids should be continued to protect the patient against adrenal failure and to maintain control of the ulcerative colitis.

Conclusions

Adrenocorticotropin and related compounds are useful adjuncts to the conventional treatment of ulcerative colitis and, indeed, may alter favorably the course of the disease. The administration of these powerful hormonal agents may be complicated by serious adverse effects; usually these can be prevented or treated effectively.

Summario in Interlingua

Colitis ulcerative es un serie morbo invalidante de curso variabile con remissiones e exacerbationes a non-predicibile intervallos. Le therapia medical conventional es de adjuta, sed ante le advento del therapia adrenocortical le nunc frequente obtention de resultatos frappante esseva un phenomeno plus tosto rar. In un serie de 100 casos tractate per duo del autores ante le introduction del steroides e reportate in 1948,

53 patientes beneficiava ab le therapia conventional. Dece-quatro patientes moriva. Peritonitis secundari a perforation intestinal esseva le causa de morte in nove casos. Ab 1950 usque al fin de 1955 le autores tractava un serie de 180 patientes con ACTH, cortisona, hydrocortisona, e simile compositos. Le resultatos obtenite esseva satisfactori o mesmo frappantissime in 85% del casos. Solmente 6 del 12 mortes in iste gruppo esseva possibilemente relationate con hypercorticismo. Le serie includeva un sol caso de peritonitis, e iste complication habeva su origine probabilemente ante le initiation del therapia hormonal. Recurrentia de symptomas esseva notate in 70% del casos. Le majoritate del patientes habeva habite lor morbo ab longe tempores e a grados sever. Esseva notate un decrescentia progressive del responsa a successive cursos de therapia steroide.

Sex casos es discutite in detalio pro illustrar le effectos benefic e adverse del therapia cortical. Il pare que ACTH aquose es le hormon de election. Tamen, hydrocortisona e le plus recente analogos es frequentemente efficace in uso initial. Illos es extrememente utile in prolongate therapia de mantenentia. Illos es etiam de valor como reimplaciamentos de ACTH in casos in que edema, hypertension, o disturbation electrolytic se disveloppa post un initialmente satisfactori responsa a corticotropina. ACTH in forma de gel esseva minus fidel que le preparato aquose. Le melior duration del therapia cortical non es predicibile in patientes individual, sed un continuation prolongate durante menses e mesmo annos es apparentemente desirabile in multe casos.

Le effectos adverse associate con le administration de hormones adrenal include alterationes cushingoide, edema, hypertension, alcalosis hypokalemic, psychose, e infection. Le externe alterationes cushingoide non es multo significative. Illos es neutralisabile, al minus in parte, per le reduction del dosage. Edema e hypertension occurre a grados non negligibile. Ambes pote esser reducite per le restriction drastic del ingestion de sal, per le uso de plus parve doses de ACTH, o per le substitution de prednisona o prednisolona. A causa del effecto irritative exercite per oral sales de kalium super le vias gastrointestinal, alcalosis hypokalemic es un problema plus commun e therapeuticamente plus complexe in patientes con colitis ulcerative que in individuos qui pote tolerar tal sales. Le repletion intravenose de kalium es recommendate pro patientes hospitalisate. Le risico de oral chlorido de kalium pote esser prendite in le caso de patientes ambulatori. Le plus recente analogos steroide es minus preste a producer disequilibrio electrolytic. Psychose non es commun sed representa un serie complication del therapia cortical. Reduction del dose e le uso de sedativos, incluse le agentes tranquillisante, es indicate al prime signos de disturbation de comportamento. Un episodio francamente psychotic necessita abstention del therapia hormonal. Felicemente, exacerbation del colitis non es un occurrentia usual sub iste conditiones. Infectiones disseminate es le minus commun del mentionate effectos adverse. Intense therapia antibiotic es indicate. Le uso del corticoides es a continuar pro proteger le patiente contra disfallimento adrenal e pro mantener le impacto super su colitis ulcerative.

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THE DEMONSTRATION OF MALIGNANT CELLS EXFOLIATED FROM THE PROXIMAL COLON *

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Introduction

Despite the widespread application and popularity of the cytologic diagnosis of cancer, there has been relatively little interest in utilizing this technic for the demonstration of carcinomatous lesions of the large bowel. The apparent reason for this lack of emphasis has been the obvious difficulty encountered in the collection of cells. Certainly the time-honored clinical methods used in the detection of colonic carcinoma have left much room for improvement, especially in cases where the tumor has been located beyond the reach of the sigmoidoscope.

The previously reported work is scant. Significant contributions by others will be mentioned briefly. Loeb and Scapier in 1951 described a technic of making their saline washings directly from visible lesions during sigmoidoscopy.[1] In 1952 Bader and Papanicolaou reported the results of 200 rectal washings obtained by the same technic and 24 colonic washings obtained by saline enemas.[2] These investigators felt that they had achieved satisfactory collection and preservation of cells and that they had demonstrated malignant cells with a high degree of accuracy. In 1953 Rubin and his co-workers described the findings in 33 patients with large bowel carcinoma, 27 of whom had correct cytologic diagnoses.[3]

The primary concern of this clinic and laboratory has been the demonstration of malignant cells exfoliated from that portion of the colon beyond the range of a 25 cm. sigmoidoscope. Patients with visible lesions of the distal colon or rectum have served as positive controls. Positive malignant smears have been obtained in virtually 100% of these patients.

The present paper is concerned with the cytologic diagnosis of carcinoma of the colon in eight selected patients: four with carcinoma of the cecum or ascending colon, two with carcinoma of the hepatic flexure, and two with carcinoma of the descending colon. The lesions localized in the descending colon are included in this study since the tumors were beyond the range of a 25 cm. sigmoidoscope.

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Technic

The patient is instructed to take a light meal the evening prior to examination. On the following morning warm tap-water enemas are administered to the fasting patient until the returns are clear.

Shortly after the enemas the patient is placed in the left lateral decubitus position. A lubricated (Lubritine Jelly—Abbott) No. 18 Fr. rubber catheter is inserted rectally to a level of 10 to 20 cm. Approximately 250 ml. of unheated 0.9% saline are poured into the bowel, utilizing a glass funnel attached to the catheter. The catheter is clamped and the patient placed on his back. The abdominal wall overlying the large intestine is massaged with deep pressure and the patient is rotated into the right lateral decubitus position. After several minutes he is rotated gradually back to the left lateral decubitus position and the saline is collected by siphonage into a clean specimen bottle. The entire procedure requires about 15 minutes.

An alternate technic provides for lavage of the colon immediately following sigmoidoscopy. Saline is funneled into the bowel while the patient is in the jackknife position. After several minutes the saline is collected by siphonage merely by tilting the examining table.

Immediately following collection of the saline washing, it is spun in a centrifuge at 1,000 r.p.m. for about 35 minutes, using three or four balanced 50 ml. centrifuge tubes. The sediment is smeared on four glass microslides previously cleansed with alcohol and labeled. Immediately after preparation of the smear, each slide is dropped into a fixative solution of equal parts ethyl ether and 95% ethyl alcohol. Fixation requires 12 hours.

Following fixation, the smears are stained with hematoxylin free of acetic acid and the Counterstains Orange G-6 * and EA-50.* The smears are dehydrated and cleared, cover-slips are mounted with Canada balsam and the entire slide is cooked briefly on a hot plate to harden the balsam. After careful survey of each slide, suspicious or positive tumor cells are suitably marked for subsequent confirmation by the cytopathologist.

Smears are reported as: (1) positive, consistent with adenocarcinoma; (2) doubtful; (3) negative, or (4) unsatisfactory. An unsatisfactory report connotes a paucity of cells for diagnosis or technical inadequacy of the prepared smear.

Large Bowel Cytology

Normal or Nonmalignant Cytologic Findings: The large intestine is lined with a simple epithelium consisting of columnar cells and interspersed goblet cells. This surface epithelium is continuous with the epithelium of the crypts of Lieberkühn, where the goblet cells are more numerous. Although this surface epithelium exfoliates freely, only a few cells of large

* Ortho Pharmaceutical Corporation.

bowel washings are well preserved. Most cells show striking degenerative changes.

Because of the simplicity and uniformity of colonic epithelium and the absence of exfoliated cells from other organs, the cytologic aspects of large bowel washings are elementary. Normal cells are unusually consistent in morphologic design, a fact which makes malignant cell structure all the more outstanding (figure 1).

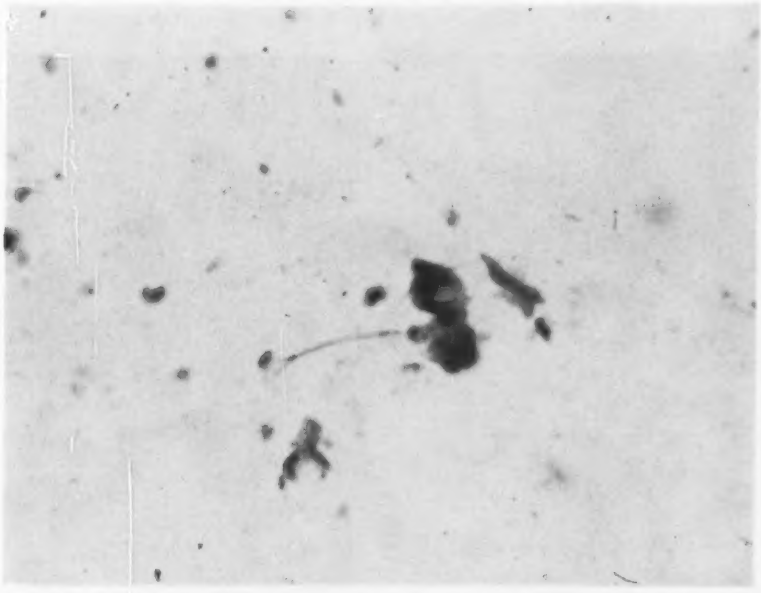

FIG. 1. A cluster of moderately well preserved normal columnar cells in a smear from a large bowel washing.

Malignant Cytologic Findings: Usually malignant cells from colonic adenocarcinoma stand out in striking contrast to the relatively uniform normal cells. Malignant cells are larger and show nuclear changes characteristic of cancer. Clusters of cells, if present, demonstrate crowding, irregular pattern and loss of polarity. The cytoplasm is poorly preserved and cellular borders indistinct. Nuclei often show enlargement, elongation and hyperchromasia. Frequently this elongation of nuclei appears at a relatively early stage of large bowel malignant lesions (figure 2).

In summary, four criteria are valuable in the recognition of malignant intestinal epithelial cells:

1. Irregularity of the chromatin network and an increase in the chromatin content of the nuclei.

2. Condensation of chromatin at the nuclear borders.
3. Absence of cellular borders and inadequate amounts of cytoplasm.
4. Variation in size and shape of the cells, particularly of the nuclei.

Case Reports

Case 1. The patient was a 71 year old white male farmer.

Pertinent History and Physical Findings: Anemia, weight loss, anorexia and generalized abdominal distress of less than one year's duration. Pallor and a tubular mass deep to a McBurney scar.

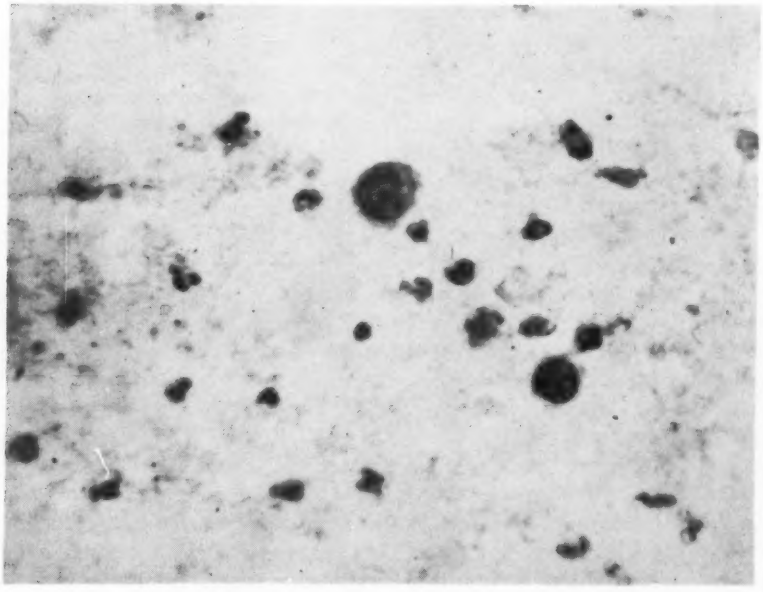

Fig. 2. The two largest cells are malignant cells obtained by colonic washing. The smaller cells are mononuclear phagocytes and degenerate columnar cells.

Pertinent Laboratory Findings: Stools positive for blood; hemoglobin, 6.0 gm.%.

X-ray Findings: (1) Barium enema (10–14–53); suspected cecal lesion, indefinite. (2) Repeat barium enema; no lesion demonstrated.

Operation (10–27–53): Inoperable carcinoma of the cecum.

Cytologic Findings (11–6–53): Positive for malignant cells (figure 3).

Case 2. The patient was a 68 year old white housewife.

Pertinent History and Physical Findings: Gross red blood per rectum, five months' duration; midabdominal pain, three weeks' duration. Obesity. Suspected mass in right lower quadrant of the abdomen.

Laboratory Findings: Stools negative for occult blood; hemoglobin, 7.8 gm.%.

X-ray Findings: (1) Barium enema (11–25–53), suspected cecal lesion; diverticula of descending colon.

Cytologic Findings (11–30–53): Positive for malignant cells.

Operation (12–3–53): Adenocarcinoma, cecum, with regional lymph node metastases.

Case 3. The patient was an 82 year old white housewife.

Pertinent History and Physical Findings: Bright red blood per rectum for one week six months prior to admission; recurrence of bleeding on the day of admission. Pallor. Examination otherwise negative.

Laboratory Findings: Stools positive for occult blood; hemoglobin, 7.8 gm.%.

X-ray Findings: (1) Barium enema (4–13–54), suspected cecal polyp; diverticulosis, descending colon. (2) Barium enema (4–23–54), no cecal polyp; diverticulosis, descending colon. (3) Barium-air contrast enema (4–29–54), negative.

Cytologic Findings (4–14–54): Positive for malignant cells.

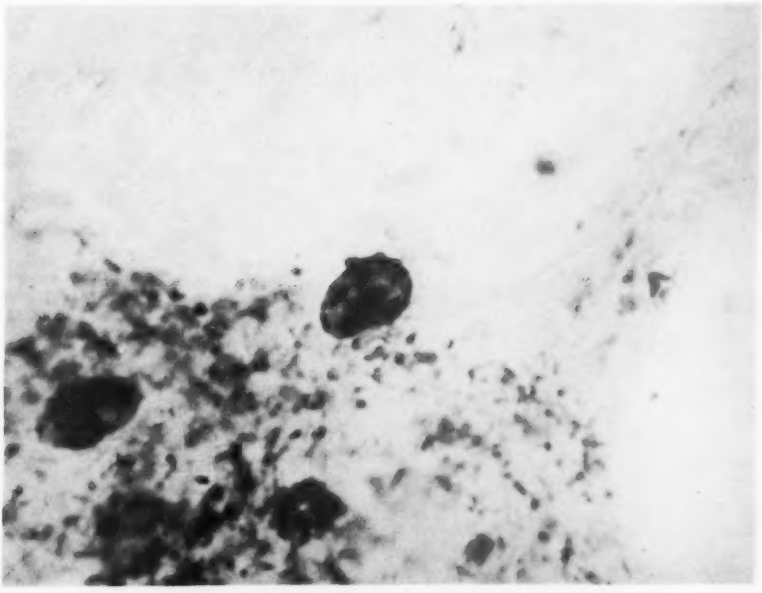

FIG. 3. Two large malignant cells obtained by colonic washing in case 1. This patient had carcinoma of the cecum.

Operation: Declined. (In this present series, this is the only case lacking pathologic confirmation.)

Case 4. The patient was a 71 year old white housewife.

Pertinent History and Physical Findings: Shortness of breath and anemia, five months' duration. Pallor and hepatomegaly.

Laboratory Findings: Stools positive for blood; hemoglobin, 6.4 gm.%.

X-ray Findings: (1) Barium enema (4–15–53), negative. (2) Barium-air double contrast enema (4–21–53), negative.

Eight months later: Re-admitted to the hospital for the same problem.

X-ray Findings: (3) Barium enema (2–18–54), "napkin ring" defect of ascending colon.

Cytologic Findings (2–20–54): Positive for malignant cells.

Operation (2–25–54): Adenocarcinoma of ascending colon, lesion 5 cm. diameter.

Case 5. The patient was a 71 year old white housewife.

Pertinent History and Physical Findings: Weakness, five months' duration; diarrhea, four months' duration. Mass 8 cm. in diameter in right lower quadrant of the abdomen. Pallor.

Laboratory Findings: Stools positive for occult blood; hemoglobin, 5.9 gm.%.

X-ray Findings: Barium enema (4–27–54), carcinoma of hepatic flexure.

Cytologic Findings (5–5–54): Positive for malignant cells (figure 4).

Operation (5–10–54): Adenocarcinoma, colon; no metastases noted.

Case 6. The patient was a 53 year old Negro male janitor.

Pertinent History and Physical Findings: Acute, bright red bleeding per rectum on the day of admission. Examination negative.

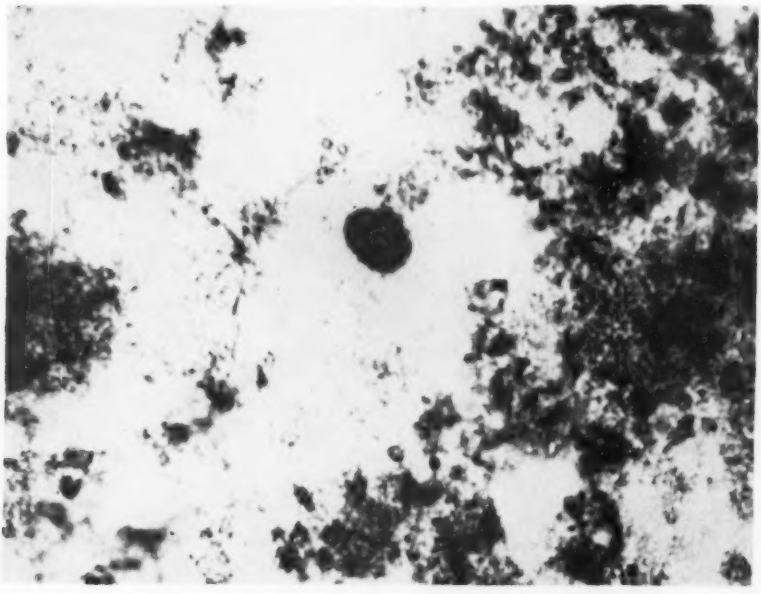

FIG. 4. A single large malignant cell surrounded by amorphous material, obtained by colonic washing in case 5. This patient had carcinoma of the ascending colon at the hepatic flexure.

Laboratory Findings: Stool positive for occult blood; hemoglobin, 9.7 gm.%.

X-ray Findings: (1) Barium enema (10–2–53), negative. Upper gastrointestinal series negative.

The patient was discharged and remained well for six months. Acute rectal bleeding recurred. The findings upon re-admission were unchanged.

X-ray Findings: (2) Barium enema (3–12–54), suspected carcinoma of hepatic flexure and sigmoid colon. (3) Barium-air double contrast enema (3–14–54), hepatic flexure normal; no definite lesion. (4) Barium enema (3–27–54), carcinoma, hepatic flexure.

Cytologic Findings (3–17–54): Positive for malignant cells (figure 5).

Operation (5–3–54): Adenocarcinoma, 4 to 5 cm. diameter, involving transverse colon near hepatic flexure; metastases demonstrated in regional lymph nodes.

Case 7. The patient was a 61 year old white housewife.

Pertinent History and Physical Findings: Acute rectal bleeding. Physical examination negative.

Laboratory Findings: Stools positive for occult blood; hemoglobin, 11.6 gm.%.

X-ray Findings: (1) Barium enema (7–30–53), negative. (2) Barium-air double contrast enema (8–7–53), negative.

The patient was discharged; *five months later,* recurrent acute rectal bleeding. The findings on admission were unchanged.

X-ray Findings: (3) Barium enema (12–8–53), suspected sigmoid defect. (4) Barium enema (12–10–53), probable small polypoid lesion in sigmoid colon.

Cytologic Findings (12–5–53): Positive for malignant cells (figure 6).

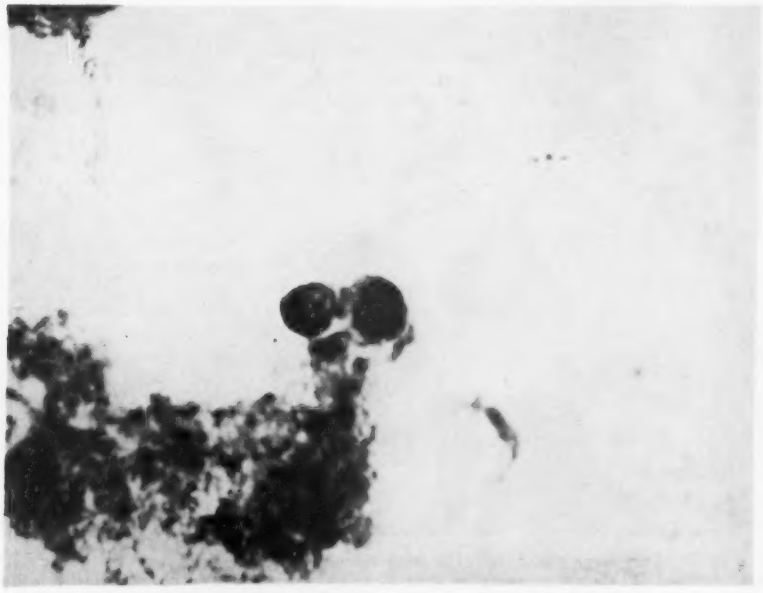

FIG. 5. Two large malignant cells near a clump of amorphous material, obtained by colonic washing in case 6. This patient had carcinoma of the transverse colon at the hepatic flexure.

Operation (12–14–53): Annular carcinoma, terminal portion of descending colon involving two thirds of the circumference of the bowel. There were no demonstrable metastases.

Case 8. The patient was a 54 year old white housewife.

Pertinent History and Physical Findings: Bloody and black stools of several months' duration; occasional left lower quadrant abdominal pain. Arterial hypertension; cardiac enlargement; tender, oblong mass, 5 cm. by 10 cm., in the left lower quadrant of the abdomen.

Laboratory Findings: Stools positive for occult blood; hemoglobin, 11.9 gm.%.

X-ray Findings: Barium enema (5–28–54), annular carcinoma, lower descending colon.

Cytologic Findings (6–8–54): Positive for malignant cells.

Operation (6–10–54): Adenocarcinoma, lower descending colon, with invasion of mesentery.

Conclusions

Malignant lesions of the colon are particularly amenable to diagnosis by cytologic technics. The procedure is especially helpful when the clinical impression of cancer of the colon is indefinite or unconfirmed by suitable roentgenologic technics.

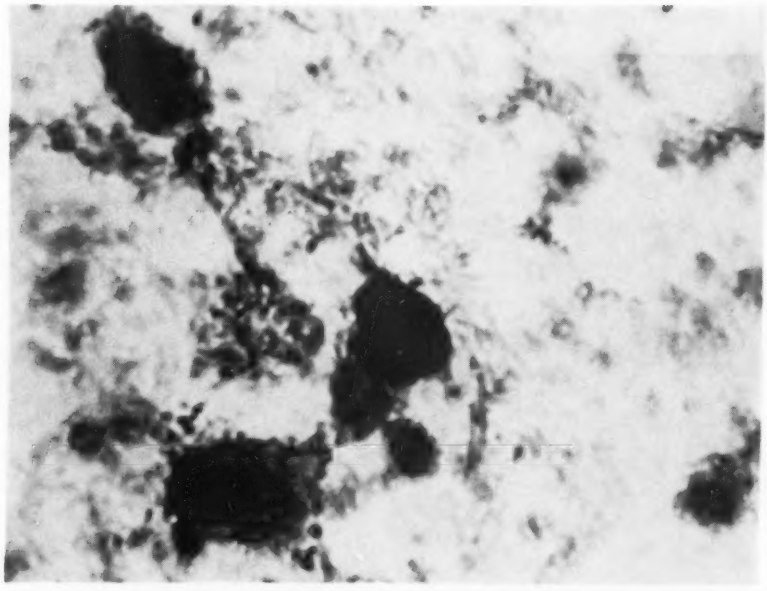

Fig. 6. Two large malignant cells with extremely dense nuclei near the center of the field, obtained by colonic washing in case 7. This patient had carcinoma of the terminal portion of the descending colon.

It is feasible to demonstrate, consistently, malignant cells exfoliated from carcinomatous lesions of the proximal colon. Appropriate cellular preparations are obtained by small volume saline washings.

Although the problem of positive smears in the absence of corroborative evidence has not been the subject of the present discussion, it is our conviction that such patients deserve repeated cytologic and roentgenologic studies under suitable conditions. The incidence of false-positive smears is of negligible significance.

Summario in Interlingua

Le diagnose cytologic de cancere es specialmente importante in casos de lesiones carcinomatose del colon in areas non accessibile al sigmoidoscopio quando methodos

clinic e radiologic se ha provate inadequate. Le publicate reportos de studios de iste problema es pauco voluminose, e le publicationes que existe describe principalmente le cytologia de lesiones que es visibile per le sigmoidoscopio.

Le presente studio concerne le demonstration de maligne cellulas exfoliate ab lesiones carcinomatose que es non accessibile per medio del sigmoidoscopio. Iste cellulas es colligite ab le mundate colon in lavages a parve volumine de solution salin de 0,9%. Le apparentia de illos es multo distincte, proque in cellulas del grande intestinos le characteristicas de malignitate es prominente.

Es describite le technica del collection, preservation, e demonstration del cellulas. Le criterios cytologic de malignitate es presentate. Photographias servi a illustrar cellulas normal e cellulas maligne.

Es presentate breve descriptiones de octo casos seligite. Quatro habeva carcinoma del ceco o del colon ascendente. Duo habeva carcinoma del flexura hepatic. Duo habeva carcinoma del colon descendente. Nulle del lesiones esseva accessibile al sigmoidoscopio. In plures de iste casos le diagnose cytologic de cancere precedeva le completion de altere definitive reportos diagnostic.

Es stipulate como conclusion que lesiones carcinomatose del colon es specialmente apte al diagnose per technicas cytologic. Il es possibile demonstrar cellulas maligne exfoliate ab lesiones del proximalitate del ceco.

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BEZOARS *

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Bezoars, although fairly rare, are likely to pose clinical problems when they enter into the differential diagnosis of disorders causing abdominal pain, or when they are encountered by chance in x-ray examinations of the abdomen. Reports of bezoars have appeared periodically in the literature since the first case in man was described by M. Baudamant in Paris in 1779.[1]

A bezoar is a bulky mass of a type of foreign material occurring in the stomach or intestine of man or animal. It is prone to be a cause of acute or chronic disease as a result of impairment of the function of the alimentary canal.

Matas,[1] in a paper presented to the Southern Surgical and Gynecological Society in 1914, reviewed in some detail the historical background of this condition, which is first mentioned in the time of the ancient Hindus, 12 centuries B.C. Writings of that period of history describe the use of bezoar stones from goats' stomachs for medicinal purposes. Later references to the use of these stones were found in the Persian manuscripts; the Arabs likewise were acquainted with them.

The word bezoar probably had its derivation from the Arabian word *badzehr,* meaning antidote. It was believed among the ancients that great curative powers were contained in these goat balls, protecting the user from many of the ills of man. Even down to the 20th Century, among the superstitious, bezoars, known as "mad stones," have been employed in therapy. Tondreau and Kirklin [9] refer to an advertisement which appeared in a Missouri newspaper as late as 1929: "For Sale: Madstone, large enough for two."

The early bezoars described in man were trichobezoars, or hair-balls. After the report of a hair-ball in a 16 year old boy in 1779, sporadic reports of other cases appeared in the literature. In 1883 Schonborn [2] successfully removed a trichobezoar from a patient's stomach. Another type of concretion was described in 1865, when Tidemand reported a gastric mass weighing 1265 gm. and composed of shellac; and persimmon bezoars were described first in 1894.

In 1938, DeBakey and Ochsner [3, 4] published a classic paper on the subject of bezoars, reviewing comprehensively the world's literature on this subject and collecting a total of 311 cases, including their eight new cases. Since that time, additional reports in the literature have brought the total number

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of reported cases to more than 400. Undoubtedly, many others have not found their way into the medical literature.

The stimulus for this review of the subject of bezoars and concretions comes from three recent cases at Methodist Hospital, and a review of records of seven other cases seen at Methodist Hospital and Parkland Hospital from 1940 to 1954. These 10 cases are reported later in this paper.

Classification and Incidence

Bezoars have been classified into several varieties on the basis of composition. Accordingly, four types are described:

1. Trichobezoar, resulting from the ingestion of hair.
2. Phytobezoar, composed of a variety of vegetable materials.
3. Trichophytobezoar, a combination of the first two types.
4. Concretions, resulting from ingestion of such materials as gums, resins, shellac and other glutinous substances.

Clinical Manifestations

1. Trichobezoars are masses containing hair matted together in the stomach, frequently filling the stomach, but in some cases consisting of several separate hair-balls. These hair-balls usually take on the contour of the stomach, and are described as J-shaped foreign bodies in the stomach. They vary considerably in size, constituting at times enormous structures weighing up to six or seven pounds. A portion of the hair-ball may sometimes extend through the pylorus and assume the configuration of the first and second portions of the duodenum. Indeed, small portions of the hair-ball may pass through the intestinal canal and be observed in the stool. The surface of the hair-ball is usually covered over with a thick layer of mucoid, slimy material. Entrapped in the meshes of hair-mass are particles of food and fiber, giving to the hair-ball a firm consistency. These bezoars occur most commonly in the stomach, and may exist in that organ for months or years before symptoms and signs indicate the presence of a foreign object. The symptom complex usually consists of abdominal pain, nausea, weakness, loss of weight, constipation and diarrhea, and hematemesis. One or a group of these symptoms may serve as the presenting manifestation of a trichobezoar. The most important bit of information which directs attention to this condition is the history of trichophagia. Thus, awareness of this disease as a cause of chronic gastrointestinal symptoms is of importance in eliciting the history of a trichobezoar.

On physical examination, the patient with a hair-ball frequently is a malnourished, pale, restless individual. His breath may be foul, and frequently a palpable tumor mass is encountered in the examination of the upper abdominal region.

Laboratory examinations are generally of little help in the diagnosis of

this condition. A mild anemia and leukocytosis are often encountered. Gastric analysis occasionally may reveal strands of hair or other foreign materials, and stool examinations similarly may be helpful in the recovery of such particles. X-ray studies and gastroscopic examination often prove the presence of such a gastrointestinal foreign body.

2. Phytobezoars result from ingestion of vegetable and plant material of certain types. By far the most common cause of this type of bezoar is the persimmon. This type of bezoar frequently is encountered as a mass in the stomach, varying considerably in size and shape, occurring most commonly as an ovoid or spherical object in the stomach. Phytobezoars are likely to be smaller than trichobezoars, and therefore are encountered frequently in the small bowel, where they often are the cause of intestinal obstruction. This type of bezoar is usually a smooth, dark brown or black, slimy foreign substance, hard and compact, but crumbling readily, very much like putty. It contains vegetable fibers, seeds and skin.

The persimmon, which causes this type of bezoar, is a plumlike fruit of a tree of the ebony family which grows wild in the tropical and temperate zones of North and South America and Asia. The best known species in America is the common or American persimmon (*Diospyros virginiana*), which grows wild in the states between Connecticut and Iowa, and south to the Gulf Coast. The plumlike fruit contains a large amount of an astringent soluble tannin [5] which, upon ripening, undergoes a change in which the tannin becomes coagulated and insoluble. Through ripening, it loses its astringent property and becomes palatable. In the stomach, particularly an empty stomach, dilute mineral acids produce coagulation of the tannin of the fruit, resulting in a sticky precipitate, the basis for the bezoar mass.

The symptom complex which results from phytobezoars may be similar in some respects to that of a hair-ball; however, in many instances the onset of symptoms is rather abrupt, with intense upper abdominal pain. Eliciting the history of the ingestion of a plant substance capable of creating a bezoar is of greatest importance in making the diagnosis of a phytobezoar. Physical examination may reveal little. There may be a mass palpable in the upper abdominal region or evidence of small bowel obstruction. Roentgenographic studies of the gastrointestinal tract again are of great importance in demonstrating the presence of this type of bezoar.

3. Concretions usually consist of masses composed of shellac, gums, resins and similar sticky materials. They are most commonly encountered among painters and furniture workers, where furniture polishes containing strong solutions of shellac are used.[6] This type of concretion develops in individuals after the material has been ingested, usually for the alcohol content of the substance. Then, when water is introduced into the stomach, it precipitates the gummy, resinous material into a solid mass in the stomach, thereby initiating a shellac concretion. Concretions have been reported

from salol [1] ingested over a long period of time in the treatment of cystitis; from bismuth [4] for roentgenographic study of the gastrointestinal tract; and from the therapeutic use of carbonates and bismuth [4] in the treatment of peptic ulcer. Intestinal obstruction has been reported by various authors from masses in the small bowel composed of the following materials (some of which should not be classified strictly as bezoars or concretions): macaroni, mucilage, methyl-cellulose (used in the treatment of constipation), barium (for gastrointestinal x-ray studies), sand (taken for indigestion), biliary calculi, dried peach substance, celery, cherry pits, orange pulp, nail trimmings, raw carrots and chewing gum.[4, 7, 8]

Incidence of Bezoars

In their review of world literature of 1938, DeBakey and Ochsner [4] found that the incidence of trichobezoars was considerably greater than that of all other types. One hundred seventy-two of the 311 cases collected and reviewed in their series were hair-balls.

In the reports that have appeared in the literature since 1938, there have been few trichobezoars and a larger number of the various types of phytobezoars and concretions, so that, contrary to the recorded incidence statistics, it appears that phytobezoars, particularly persimmon bezoars, now are encountered more frequently than trichobezoars.

Age and Sex Incidence

The age at which bezoars are found provides a striking contrast between trichobezoars and phytobezoars. DeBakey and Ochsner found that 80% of trichobezoars occur before the age of 30 years, while only 30% of phytobezoars were found in individuals under 30 years of age.

This contrast is further developed in the comparison of the sex incidence of bezoars. DeBakey and Ochsner reported 91% of trichobezoars had been found in females, while only 23% of phytobezoars occurred in women.

These striking age and sex contrasts in the incidence of bezoars are worthy of a certain amount of emphasis. It has been pointed out that hair-balls occur characteristically in young women, and particularly in young girls who are inclined to wear their hair loose, blowing and hanging over the shoulders, a custom which predisposes to the habit of trichophagia. Matas [1] suggests an analogy between trichophagia and the habit of biting the finger nails. Numerous authors discussing the nature of trichobezoars have emphasized the importance of underlying neuropsychiatric disorders of individuals who have such bezoars.

On the other hand, phytobezoars occur typically in males above the age of 30. Men of this age group are much more likely than women to encounter persimmons in their outdoor activities, and through ingesting this fruit become subject to such phytobezoars. Likewise, men of this age

group are in occupations where certain gummy substances such as furniture polish may be encountered to serve as a source of development of concretions.

Treatment

The treatment of bezoars and concretions is, almost without exception, surgical removal of the foreign body. Conservative measures are usually inadvisable. It is important to bear in mind that, in operative removal of phytobezoars particularly, not infrequently more than one bezoar is encountered in the same patient. Thus, a thorough exploration of the stomach and small bowel is imperative to avoid later recurrence of the same disorder from a second bezoar elsewhere in the gastrointestinal tract.

Complications

Complications from bezoars are primarily a result of two factors: (1) interference with the normal physiologic activity of the gastrointestinal tract, such as intestinal obstruction or inanition; and (2) traumatic irritation of the stomach and bowel wall and its consequences of mucosal erosion, ulceration, perforation and peritonitis.

Case Reports

Case 1. A 52 year old housewife was admitted to Methodist Hospital on February 1, 1951, with the history of continuous epigastric pain, accompanied by nausea and vomiting, for two days prior to admission to the hospital. She had had no previous similar pain and no gastrointestinal symptoms. A few weeks prior to the onset of this attack of abdominal pain, however, she had eaten a few ripe persimmons.

Physical Examination: The patient was well developed and well nourished. Skin was moist, with no discoloration. Examination of the head and neck was essentially normal. No masses were palpable in the examination of the abdomen, and no enlarged organs were elicited.

Laboratory: Red blood count, 5,890,000; hemoglobin, 18.1 gm.; white blood count, 7,750, with 86% polymorphonuclear cells and 14 lymphocytes. Six days after admission to the hospital, prominent distention of the abdomen developed. At this time a scout film of the abdomen revealed gaseous distention of the small bowel in the upper abdomen and left lower quadrant of the abdomen, suggesting an obstruction in the midportion of the ileum.

At operation, a foreign body was found impacted in the midportion of the ileum, and was removed. A segment of the small bowel proximal to this obstruction was discolored and therefore resected. The patient's recovery was rapid.

Examination of the specimen revealed a dark brownish black, irregular mass, measuring 7 by 2 by 2 cm. The surface was rough and slightly bile-stained. It was found to be solid and contained fragments of vegetable material resembling persimmon substances.

Diagnosis: Phytobezoar, of persimmon type.

Case 2. A 35 year old white housewife was admitted to Methodist Hospital on December 17, 1954, after having had generalized abdominal pain for one day prior to admission. The pain was followed by the onset of nausea and vomiting, and the patient on admission was acutely ill. Past history revealed no previous episodes of

this type, and no history of melena or gastrointestinal bleeding of any form. She had ingested two or three ripe persimmons about one month before the onset of pain.

Physical Examination: Temperature, 100.6° F.; pulse, 84; respirations, 22; blood pressure, 130/90 mm. of Hg. She was well developed and well nourished, and in acute distress due to abdominal pain. Examination of the head and neck was essentially normal. Heart and lungs were normal. Abdomen was soft and flat. There was moderate tenderness in the epigastric region. No enlarged organs or masses were palpable about the abdomen. A scout film of the abdomen was thought to be normal, but on the third day after admission to the hospital, a second scout film of the abdomen showed several rather widely distended loops of the small bowel in the midabdomen and left upper quadrant, with some gas visible in the right colon as well as in the sigmoid. The amount of gas present in the small bowel was suggestive of a low grade small bowel obstruction. A barium enema following this procedure revealed no lesion in the colon, but the terminal ileum was filled, and just proximal to the ileocecal valve an ovoid mass was outlined which measured approximately 8 by 5 cm. Subsequent films showed that this mass was completely outlined by barium. This was considered to be either a bezoar or an intraluminal polypoid tumor. Films made on the following morning showed a step-ladder arrangement of loops of small bowel in the midabdomen, with moderate distention of all of these loops and with some gas visible in the transverse colon.

Laboratory: Red blood count, 4,040,000; hemoglobin 12 gm.; white blood count, 12,100, with 4 bands, 73 segmented forms, 18 lymphocytes and 5 monocytes. Urine contained a trace of albumin and many erythrocytes. Serum sodium was 151 mEq./L.; potassium, 4.4 mEq./L.; CO_2 combining power, 72 vol.%; blood chlorides, 468 mg.%.

A laparotomy on the third day revealed an obstruction about two feet from the ileocecal valve, and a foreign body was removed from this region. The specimen consisted of a large, ovoid, coarsely granular, brownish purple structure measuring 6.5 cm. in greatest diameter. When the structure was broken up it was found to be composed of amorphous, light tan material, some portions of which appeared to be the type of material seen in bezoars made up of persimmon fiber. The patient's immediate postoperative course was uneventful, but one week after she returned home a recurrence of cramping abdominal pain of brief duration supervened. Subsequent examinations have failed to demonstrate further evidence of gastrointestinal pathology.

Diagnosis: Phytobezoar, terminal ileum.

Case 3. A 39 year old white housewife was admitted to Methodist Hospital on July 2, 1952, with the history of sudden onset of a severe pain in the upper abdomen which came on while the patient was in a movie. Nausea and vomiting developed soon after the onset of this pain. There had been no previous attacks of this type, nor any other symptom to suggest a gastrointestinal disorder in the past. There had been nothing unusual about her diet in the past, and she gave no history of ingestion of persimmons.

Physical Examination: The patient was well developed and well nourished, acutely ill and in distress from severe pain in the abdomen. Blood pressure, 116/60 mm. of Hg; temperature, 98.6° F.; pulse, 76; respirations, 24. Examination of the head and neck revealed no significant findings. Heart and lungs were essentially normal to examination. Abdomen revealed moderate tenderness to palpation in the epigastric region. No masses were palpable, and no enlarged organs were detected.

Laboratory: Red blood count, 3,980,000; hemoglobin, 12 gm. White blood count, 15,250, with 1 band, 82 segmented forms and 17 lymphocytes. Urinalysis was normal except for 2 plus albumin.

At surgery the stomach was found to be dilated, as was the first portion of the

duodenum. Several large, hard objects were palpated in the second part of the duodenum. The duodenum was opened and several masses of friable material were removed from the bowel lumen in the region of the ampulla of Vater. The gall-bladder and bile duct appeared to be normal. The patient's postoperative course was uneventful, and the specimen removed from the duodenum was described as a yellow, pigmented mass consisting of several pieces, irregular in shape and varying in size from 1.2 to 0.5 cm. in diameter. On sectioning, these masses were found to be of yellow, amorphous structure. No definite vegetable fragments were identifiable grossly.

Diagnosis: Bezoar, possibly of gall-stone origin.

Discussion: This case represents obstruction of the second part of the duodenum by a concretion, possibly of biliary calculus origin; however, there was no other evidence to suggest biliary tract disease in the past or at the time of surgery. The patient's recovery was prompt and complete.

A review of Methodist Hospital and Parkland Hospital records revealed seven other cases of gastrointestinal bezoars and concretions during the years from 1940 to 1954. These are summarized below:

Case 4. A 72 year old dentist was admitted to Methodist Hospital on January 1, 1946, with an episode of upper abdominal pain of sudden onset the day of admission to the hospital, accompanied by nausea and vomiting and marked abdominal distention. This man had been well until one day prior to admission, when he had the onset of the pain. Several weeks prior to the onset of his pain he had ingested several ripe persimmons.

Physical Examination: The patient was an acutely ill elderly man, with marked abdominal distention and in acute distress from abdominal pain. Head and neck were normal, and there were no abnormal findings about the chest. There was diffuse tenderness over the abdomen, but no muscle guarding. There were prominent abdominal distention and very active peristaltic sounds. No abdominal organs could be palpated, and no masses were felt.

Laboratory: Red blood count, 6,380,000; hemoglobin, 17.8 gm.; white blood count, 18,500, with 54 segmented forms, 15 bands and 31 lymphocytes. Urine report was normal except for a trace of albumin. Blood urea nitrogen was 17.4 mg.%, and blood sugar was 96 mg.%.

Temperature ranged from 99.6° F. the first day to 101.6° F. on the third day. Gastrointestinal x-ray study the day after his admission to the hospital revealed a partial obstruction in the midjejunum. At that point the column of barium could be seen to split into two columns, which appeared to be passing around a mass in the jejunum. This was thought to be a tumor or phytobezoar. Two days after his admission to the hospital, laparotomy revealed findings of obstruction in the lower part of the jejunum, and a foreign mass was removed from the small bowel measuring 2.5 by 2.5 by 4 cm. On section, it was found to be composed of vegetable fibers and adherent fragments, characteristic of a phytobezoar. Postoperative course was uneventful.

Case 5. A 60 year old white male was admitted to Parkland Hospital on April 2, 1940, with cramping pain in the upper abdominal region but without nausea or vomiting. These symptoms had been in progress off and on for two months prior to admission to the hospital. During the two weeks prior to admission to the hospital the patient had lost about 10 pounds of weight, and had become weakened during this period of time. One week prior to admission he had collapsed at home and had vomited bright red blood. He also had noticed the passing of black, tarry stools

for several days prior to his admission. Past history revealed that, prior to the onset of the present illness, he had been perfectly well and had had no previous similar gastrointestinal symptoms.

Physical Examination: The patient was a very pale, weak, emaciated, critically ill man. There were no remarkable findings about the head and neck, and the heart and lungs were essentially normal to examination. The abdomen was flat, and there was only slight generalized tenderness. No masses or enlarged organs were palpated. Peristaltic sounds were not remarkable.

Laboratory: Red blood count, 1,410,000; hemoglobin, 30%. White blood count, 10,800, with 20 lymphocytes, 3 monocytes, 8 bands and 69 segmented forms. Urine was essentially normal. Icterus index was 4.8 units. After several blood transfusions the red blood count was 3,100,000 and hemoglobin was 59%. At this time an upper gastrointestinal x-ray study demonstrated a very large mass in the stomach, having the appearance of a foreign body, possibly a phytobezoar, and about the size of a small grapefruit. In addition, there appeared to be a large, ulcerating lesion on the lesser curvature which suggested the possibility of a gastric carcinoma. Subsequently, gastroscopic examination revealed a large, black, tarry mass, partly covered with food particles. This mass could be displaced into the upper portion of the stomach and the instrument passed around the mass into the pyloric end of the stomach. No ulcerations and no tumors were seen at any point. One month after admission to the hospital a gastrotomy was done, and the large foreign body was removed from the stomach. This specimen was described as an irregular, greenish gray mass, measuring 9 by 6.5 by 5.5 cm. in size. It was friable and appeared to contain vegetable husks, together with seeds suggesting persimmon seeds. The patient's recovery was prompt, and he was discharged two weeks after surgery in good condition.

Diagnosis: Persimmon bezoar.

Case 6. A 57 year old white male farmer was admitted to Parkland Hospital on February 9, 1941, with cramping abdominal pain, nausea and vomiting, and swelling of the abdomen for two days. Past history revealed no similar episodes of gastrointestinal pain. He had been essentially well prior to the onset of this illness.

Physical Examination: The patient was a well developed, well nourished white male, acutely ill with abdominal pain. Examination of the head and neck was essentially negative. Heart and lungs revealed no significant findings. There were generalized abdominal distention and tenderness, without evidence of ascites. There were no palpable organs or masses. The clinical impression was intestinal obstruction, and a scout film of the abdomen revealed marked distention of the proximal or mid-ileum, indicating a fairly high grade mechanical obstruction in the mid-ileum.

Laboratory: White blood count, 21,600, with 16 lymphocytes, 2 monocytes, 5 bands and 77 segmented forms. Urinalysis was normal. Blood urea nitrogen was 27 mg.%.

At surgery the small bowel was found to be distended down to a point about 18 inches from the ileocecal valve. A mass was palpable at this point in the lumen of the bowel, which was removed. The foreign body was described as an irregular, bluish green mass, 4 cm. in diameter, containing vegetable fibers consistent with the appearance of a phytobezoar. The patient recovered promptly and was discharged from the hospital 12 days after admission.

Diagnosis: Phytobezoar, probably of persimmon type.

Case 7. A 44 year old white male laborer was admitted to Parkland Hospital on October 14, 1941. History revealed that he had had a cramping pain in the abdomen off and on for a period of one year. This pain was relieved at times by taking food and drinking milk. During this period of time he had been aware of a "knot" in the pit of his stomach, which he had been able to move about from time

to time. Periodically, this knot became painful and tender to touch. For six months prior to admission to the hospital he had been bothered with intermittent attacks of nausea and vomiting. Past history revealed no significant illnesses. He had been in generally good health until one year prior to his admission.

Physical Examination: The patient was fairly well developed and well nourished and in no acute distress at the time of admission. Examination of the head and neck was essentially normal. The heart and lungs were normal. There was moderate tenderness in the epigastric region. No masses were palpable in the abdomen, and no organs were found enlarged.

Laboratory: Red blood count, 4,900,000; white blood count, 9,600, with 40 lymphocytes, 1 monocyte, 1 eosinophil, 5 bands and 53 segmented forms. Urinalysis was normal. Gastric analysis revealed 38° free hydrochloric acid. On October 15 an x-ray study of the upper gastrointestinal tract suggested the presence of a phytobezoar. Gastroscopic examination disclosed a large black mass, freely movable in the stomach. It appeared to be approximately 4 by 10 cm. in size, and had the appearance of a phytobezoar.

Gastrotomy was done on October 18, and the foreign body, measuring 10 by 5 by 5 cm., was removed from the stomach. This specimen was a bile-stained, nodular mass, containing vegetable particles characteristic of a phytobezoar. The patient's recovery was rapid, and he was discharged from the hospital on November 1, 1941.

The case summary brought out the history of ingestion of persimmons some time prior to the onset of symptoms of this illness.

Case 8. A 61 year old white male farm laborer was admitted to Parkland Hospital on March 22, 1944, with a history of severe pain in the stomach region for three days, followed by the passing of several black, tarry stools and the vomiting of bright red blood. For an indefinite time prior to the onset of the pain this man had had brief spells of sharp epigastric pain, not very severe. This pain was worse when his stomach was empty, but it also was accentuated by eating onions, cabbage, beans or pickles. He obtained a measure of relief after the eating of his meals. There was no past history of melena or of hematemesis.

Physical Examination: The patient was a well nourished white man, not acutely ill. His blood pressure was 128/70 mm. of Hg, and the physical examination was essentially normal. There were no significant findings about the abdomen.

Upper gastrointestinal x-rays revealed a filling defect in the midportion of the stomach, suggesting carcinoma of the stomach. One week later this filling defect was visualized again, and was thought to be an intrinsic neoplasm of the stomach with an active ulcer in the first part of the duodenum. A third upper gastrointestinal x-ray study demonstrated this filling defect in the stomach, and at this time it was found to be freely movable. A foreign body could be displaced upward into the fundus of the stomach, and it was thought to be a phytobezoar. Gastroscopic examination done following the second upper gastrointestinal x-ray study revealed a large, round, smooth, tarry-black mass, freely movable in the stomach, typical in appearance of a phytobezoar.

Laboratory: Red blood count, 1,660,000; hemoglobin 5.5 gm. White blood count, 10,000, with 66 polymorphonuclear cells and 34 lymphocytes. Urinalysis was normal. Kline test was negative. Blood urea nitrogen was 60 mg.%; blood sugar, 120 mg.%; serum albumin, 3.3 gm.%; globulin, 1.1 gm.%; total protein, 4.4 gm.%. Tests for occult blood in stool were 4 plus. A gastric analysis was normal.

After several blood transfusions a gastrotomy was done, and a large, dark mass, the size of a baseball, and having the characteristics of a phytobezoar, was removed from the stomach. The patient's recovery was uneventful. The specimen removed from the stomach was described as a large ovoid mass, irregular in outline, with a smooth, irregular surface. It was black in color, but when portions of the outer

covering were removed, a brownish type of granular material was noted. The mass measured 6 by 6 by 4 cm. It was firm in consistency and rather friable. Additional history revealed that this man had eaten persimmons in the fall preceding this illness, six or seven months before.

Diagnosis: Phytobezoar.

Case 9. A three year old Negro male, admitted to Parkland Hospital on December 1, 1948, had been in good health until four days prior to admission, when he began to refuse his food, and then had the onset of intermittent attacks of upper abdominal pain. The day preceding the onset of symptoms the child had been observed eating several whole persimmons, the exact number not known. He had intermittent abdominal pain, along with constipation and vomiting, for the three days prior to his admission to the hospital. Past history revealed that he had been in generally good health up to this time.

Physical Examination: Blood pressure, 98/50 mm. of Hg; temperature, 100° F.; respirations, 24. The patient was a well developed, well nourished child, small for his age, who appeared acutely ill. Head and neck were not remarkable. Heart and lungs were normal to examination. The abdomen was found to protrude moderately, and there was generalized tympany on percussion of the abdomen. In the left upper quadrant of the abdomen there was palpable an irregular, firm mass, medial to the midclavicular line and extending almost to the midline. This mass was firm and slightly movable, and the examining hand could be inserted between the costal margin and the mass. The examination otherwise was not remarkable.

Laboratory: White blood count, 10,200, with 1 eosinophil, 4 bands, 36 segmented cells and 59 lymphocytes. Hemoglobin, 10 gm. Urinalysis was normal. Sickle cell study revealed no evidence of sickling.

At surgery the stomach was found to contain a large, firm mass, which was removed through a transverse incision in the anterior wall of the stomach. The patient's recovery was uneventful. The specimen was described as a gritty, granular mass, brown in color and measuring 9 by 5 by 4.5 cm. The surface of the mass was seen to contain a few hairs.

Diagnosis: Phytobezoar of persimmon type.

Case 10. A 14 year old Negro male was admitted to Parkland Hospital on March 13, 1949, with history of cramping epigastric pain for four days prior to the admission, accompanied by constipation and general lethargy. History revealed that he had eaten persimmons in the late summer prior to this hospital admission, six or seven months earlier. Past history revealed that he had been in generally good health prior to the onset of this illness.

Physical Examination: Pulse, 100; blood pressure, 110/84 mm. of Hg; respirations, 24. The patient was a fairly well developed, well nourished Negro male who appeared stuporous on admission. Skin was warm and dry, and skin turgor was poor. Examination of the head and neck was essentially negative. Heart and lungs revealed no significant findings. Abdomen was tense and tympanitic to percussion. Peristaltic sounds were high-pitched and infrequent. No masses or organs were palpable. The entire abdomen was tender to palpation, particularly in the epigastrium. A scout film of the upper abdomen showed considerable distention of the small intestine overlying the upper left abdominal quadrant, with one distended loop swinging across the lower abdomen, and numerous fluid levels visualized. This was considered to be a result of mechanical intestinal obstruction of the small bowel.

Laboratory: White blood count, 13,500, with 4 juvenile forms, 26 bands, 56 segmented forms and 14 lymphocytes. Hemoglobin was 10 gm.

At operation the small bowel was found to be greatly dilated above the point of obstruction in the middle third of the ileum. At this point a hard mass was palpable in the lumen of the small bowel. The foreign mass was removed, and the post-

operative course was uneventful. Examination of the foreign body revealed a mass 4 cm. in diameter which cut with moderate resistance, and with an orange surface. The mass had characteristics highly suggestive of persimmon fibers.

Diagnosis: Phytobezoar of persimmon type.

Discussion

In nine of the 10 cases presented the foreign bodies removed from the gastrointestinal tract had physical characteristics which resulted in their identification as persimmon bezoars. There was the history of recent ingestion of persimmons to verify the nature of the bezoar in seven of the cases. One case revealed a foreign substance resembling a phytobezoar in which there was no history of ingestion of persimmons or of other vegetable matter which might serve as the origin of a bezoar. This case may be the result of gall-stone impaction in the lumen of the duodenum near the ampulla of Vater, and therefore not a true bezoar. No case of trichobezoar was encountered.

In the experience with bezoars at the two hospitals, it is apparent that the persimmon bezoar is the type most commonly seen in this locality. This is unique when compared with the incidence figures in some reviews of bezoars in the medical literature, and serves to emphasize the relative frequency of the phytobezoar in the persimmon belt.

Four of this group of phytobezoars developed in the stomach, four were found in the ileum, and one each occurred in the duodenum and jejunum. Phytobezoars vary considerably in size, and the smaller ones are inclined to pass through the pylorus and to find a permanent location in the small bowel. This happens much less frequently in the case of hair-balls, most of which are found in the stomach.

To a certain extent, the location of the bezoar in the gastrointestinal tract determines the presenting signs and symptoms. In all 10 cases, pain in the abdomen was a prominent symptom. The pain was of cramping character and accompanied by signs of intestinal obstruction in all of the six cases where bezoars were located in the small bowel. In all of these cases the pain had been of brief duration, ranging from a few hours to four days. Anemia was present in only one of these six cases, and in none was gastrointestinal hemorrhage apparent.

Pain was also a complaint in the four cases of gastric bezoars, but in these cases it was described variously as cramping pain, sharp pain, and a sensation of a "knot in the stomach region." The duration of pain was two weeks to one year in this group of patients. Anorexia, weight loss and a palpable mass in the stomach region were symptoms, along with abdominal pain. Two of the four exhibited melena and hematemesis, and all four had moderate to severe grades of anemia.

X-ray studies were made in nine of the 10 cases and in every instance demonstrated evidence of a mass in the stomach or small bowel, or signs indicating small bowel obstruction. In all four of the gastric bezoar cases,

upper gastrointestinal x-ray studies revealed a mass in the stomach. Gastroscopic examination was made in three of these and demonstrated clearly the nature of the gastric mass. It is therefore apparent that x-ray procedures and gastroscopy are of great importance as diagnostic tools in the study of these cases.

Recovery was complete in all 10 of these patients after surgical removal of the bezoars. In only one case was there recurrent abdominal pain after surgery, and additional studies failed to reveal evidence of other bezoars in this case.

Summary

1. Persimmon ingestion is the outstanding cause of bezoars in geographic areas where this fruit is grown. Nine additional phytobezoars of this type have been reported in this review.

2. Phytobezoars occur most commonly in men over 30 years of age, while hair-balls are seen more frequently in young women under age 30.

3. Persimmon bezoars located in the small bowel are likely to have the presenting manifestation of signs and symptoms of intestinal obstruction, while gastric bezoars cause gastric pain, anorexia, weight loss, inanition, palpable tumor mass, and gastrointestinal hemorrhage with consequent anemia.

4. Of greatest importance in the diagnosis of bezoars is the history of ingestion of persimmons or other glutinous substances in the case of phytobezoars, or trichophagia in trichobezoars.

5. X-ray studies of the gastrointestinal tract and gastroscopic examinations are of great help in detecting and identifying bezoars.

6. Discovery and surgical removal of bezoars is usually followed by prompt and complete recovery of the patient.

Summario in Interlingua

Bezoares, ben que satis rar, debe esser contate inter le varie causas de dolores abdominal. Es presentate in iste articulo un revista del thema de bezoares. Trichobezoares, i.e. ballas de capillos, occurre plus frequentemente in juvene feminas. Phytobezoares ha lor plus alte frequentia in homines de plus que 30 annos de etate.

Le ingestion de prunas-dactylos (le fructos de *Diospyros virginiana*) es le principal causa de phytobezoares. Iste facto es illustrate per le 10 casos presentate in iste reporto ab le Hospital Methodista e le Hospital Parkland in Dallas, Texas.

In omne iste 10 casos il se tractava de phytobezoares, e nove habeva resultate ab le ingestion de prunas-dactylos. Isto servi a sublinear le importantia del pruna-dactylo como causa de bezoares in areas ubi iste fructo es cultivate o alteremente consumite como nutrimento. Nulle caso de trichobezoares esseva trovate al duo mentionate hospitales durante le periodo del presente reporto (1940 a 1954).

Un factor de grande importantia in le diagnose de bezoares es le historia de ingestion de prunas-dactylos o de altere substantias glutinose in le caso de phytobezoares o un historia de trichophagia in le caso de trichobezoares.

Bezoares a pruna-dactylo locate in le intestino tenue manifesta lor presentia generalmente per le signos e symptomas de obstruction intestinal, durante que bezoares

gastric causa dolores in le stomacho, anorexia, perdita de peso, inanition, palpabile massas tumoric, e hemorrhagias gastrointestinal con consequente anemia.

Le discoperta e ablation chirurgic del bezoares es usualmente sequite per un prompte e complete recuperation del patiente.

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CARCINOMA OF THE PROXIMAL THIRD OF THE STOMACH: A CRITICAL STUDY OF CLINICAL OBSERVATIONS IN 74 CASES *

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CARCINOMATOUS lesions located in the proximal third of the stomach present certain features which set them apart from lesions more distally situated. There are differences in pathology, symptomatology, the facility of diagnosis and, perhaps, in prognosis.

In an earlier communication [1] we reported the significantly greater difficulty of x-ray diagnosis of carcinoma of the proximal third of the stomach compared to lesions in the distal portions. While surveying the case material we were impressed with certain clinical differences relating to the sites of the lesions.

We are presenting the clinical findings in 74 cases of histologically proved adenocarcinoma of the proximal third of the stomach treated at The New York Hospital in the years 1947–1952. In every case the lesion in the stomach was confined to the proximal third at operation or at autopsy. It proved impractical to attempt further localization to specific areas within the proximal third, such as the fundus or the cardia proper. The results of our study are summarized in tables 1 through 10.

RESULTS

Age, Sex and Race: As seen in table 1, the ratio of males to females is almost 3:1, and the age range is very wide. This corresponds to figures reported on gastric carcinoma in all sites.[2–5] Few cases (14%) of carcinoma of the proximal third occurred in people under age 50. Jemerin and Colp,[3] in a study of 344 cases of gastric carcinoma, reported that 24% were seen in patients under 50 years of age. Our two youngest patients were women under 38 years of age; however, in the entire series there was no significant sexual difference in the age distribution. These findings tend to substantiate the observation that gastric cancer in the young is generally seen in women, and that proximal lesions are more often seen in older people.[6] Seventy-two patients were white, one was a Negro and one a Japanese. This distribution corresponds roughly to the hospital population.

Symptoms and Physical Findings: In the large majority of the cases the

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first symptom was either pain or dysphagia (table 2). Three patients were entirely asymptomatic. The diagnosis was made in two of these three cases on gastrointestinal x-ray examination done because of anemia (one a case of pernicious anemia), and in the third patient as an incidental finding at autopsy. (The patient died following cholecystectomy for cholelithiasis.)

In series of cancer of the stomach irrespective of site, dysphagia is a much less common first symptom than in lesions confined to the proximal third, but pain is seen with equal frequency and is the most common first symptom in both groups.[2, 4] The duration of symptoms varied widely.

TABLE 1

Age and Sex Distribution

Age in Years...	Total	Less than 40	40–49	50–59	60–69	70+
Male	54	0	7	19	14	14
Female	20	2*	1	5	7	5
Total	74	2	8	24	21	19

* Age 32, 38.

Four patients had had symptoms for more than one year. Less than 10% of the cases were seen within one month of the onset of symptoms. Patients with dysphagia tended to present themselves at the hospital somewhat earlier than those with other symptoms.

Table 3 shows the nature of the symptoms and physical findings and their frequency of occurrence. Pain and weight loss each occurred in about 75% of the cases, and they were absent together only 5% of the time (four cases). Abnormal physical findings were infrequent. Almost half the cases presented entirely normal physical examinations, and most of the remainder showed merely evidence of weight loss. The only significant dif-

TABLE 2

First Symptom with Duration Prior to Admission to Hospital

First Symptom	No.	Duration in Months			
		Less Than 1	1–6	7–12	More Than 12
Pain	35 (47%)	3	15	17	—
Dysphagia	19 (26%)	1	14	3	1
Flatulence	6 (8%)	1	3	1	1
Weakness	6 (8%)	—	3	2	1
Hematemesis	3 (4%)	1	—	1	1
Anorexia	2	—	1	1	—
Hiccups	1	—	—	1	—
Vomiting	1	1	—	—	—
Regurgitation	1	—	—	1	—
Total	74*	7	36	27	4†

* Three patients had multiple first symptoms; however, three other patients were asymptomatic and are not included in this tabulation.

† Duration, 15, 18, 18, 36 months.

TABLE 3

Symptoms and Physical Findings in 74 Patients

Symptoms	No. of Patients	Physical Findings	No. of Patients
Pain	56	Entirely negative physical examination	35
Weight loss (more than 10 lbs.)	55	Cachexia	19
Weakness	45	Enlarged liver	12
Dysphagia	36	Abdominal tenderness	10
Anorexia	35	Abdominal mass	8
Vomiting	35	Pallor	4
Flatulence	34	Jaundice	1
Constipation	22	Sentinel node	1
Belching	20	Horner's syndrome	1
Melena	19		
Nausea	19		
Hematemesis	11		

Other symptoms included heartburn, abdominal distention, hiccups, diarrhea, vertigo, fatty food intolerance, arthralgia and fever.

A history of peptic ulcer was elicited in four patients.

ferences observed from patients with gastric carcinoma irrespective of site were the relative increase in frequency of dysphagia and the markedly reduced incidence of a palpable abdominal mass in patients with involvement of the proximal third. Dysphagia is seen in 49% of proximal third cases, in comparison with 11 to 20% [2, 3] in the generality of patients with gastric

TABLE 4A

Laboratory Findings

Blood Count		Stool Guaiac Test*			Reëxamination after Initial Negative Examination		
		Initial Examination					
	No. Cases	No. Cases	+	−	No. Cases	+	−
Not done	1						
Normal	38	28	8	20	15	5	10
Anemia present†	35	31	16	15	12	5	7
(Severe anemia)†	(6)	(6)	(4)	(2)	(2)	(2)	(0)
Total	74	59	24	35	27	10	17

* Stool guaiac + indicates 2 plus or more.

† Anemia indicates less than 12 gm. hemoglobin, or less than 4 million RBC. Severe anemia indicates less than 7.5 gm. hemoglobin, or less than 2.5 million RBC.

carcinoma. An abdominal mass is palpable in only 11% of proximal third patients, in comparison with 45% to 48% [2, 5] of all cases.

Pain was usually localized to the epigastrium, but was occasionally present in other regions of the upper abdomen or in the chest. Radiation to the back or chest was infrequent. No typical pain pattern could be discerned. The severity varied from mild to severe; in some cases pain was present continuously, in others intermittently. The various descriptive adjectives used

were: dull, sharp, aching, sticking, tearing, burning, soreness and pressure. In 26 cases the relationship of the pain to eating was recorded. In 24 of these the pain was made worse by food; in only two cases was the pain relieved. This is in marked contrast to the typical pain-food-relief pattern seen in benign peptic ulcer. La Due et al.[2] note that carcinoma of the cardia can simulate angina pectoris; this was not noted in any of our patients.

Laboratory Findings: The findings on laboratory examination are summarized in tables 4A and 4B. Anemia was present in about half the cases but was rarely very severe. It was usually hypochromic in type but was occasionally normochromic or hyperchromic. The average color index was 91, with a range of 44 to 120. These findings approximate those reported for all gastric carcinomas.[2-5]

In patients with anemia, occult blood is usually found in the stool by the guaiac test. This is particularly true in patients with severe anemia, and suggests that bleeding into the gastrointestinal tract is an important cause of the anemia. However, some cases have persistently negative stool guaiac

TABLE 4B

Laboratory Findings

Gastric Acidity		Papanicolaou Study on Gastric Contents	
	No. Cases		No. Cases
0 free acid	22	Negative (Classes I–III)	12
Free acid 1–50 units	5	Positive (IV–V)	21
Free acid more than 50 units	5	Total patients examined	33
Total patients examined	32		

examinations, which suggests that the etiology of the anemia is other than blood loss. This is consistent with the recent demonstration of increased hemolytic activity in patients with various types of carcinoma.[7]

As a diagnostic test, or even an exclusion test of gastric cancer, the stool guaiac examination is very unreliable. In our patients it was positive less than half the time (41%) on the initial examination and, when initially negative, it usually remained negative on reëxamination. For all patients with gastric carcinoma, the reported percentage of positive guaiac tests on stool examination was higher.[3, 5]

Achlorhydria was found in about two thirds of the examined patients in our group. This corresponds very closely to all patients with gastric carcinoma.[2-4] Gastric carcinoma occurs three to four times more frequently in patients with achlorhydria than in acid secreting individuals of comparable age.[8] However, free acid and even high acidity do not rule out the presence of gastric carcinoma.

Papanicolaou cytologic study of the gastric contents is of definite diagnostic value. A positive finding of malignant cells was obtained in almost two thirds (64%) of the cases tested, and was sufficient to establish the di-

agnosis of gastric cancer. Only one of the seven cases tested by the recently developed abrasive balloon technic was negative.[9] As this technic is more widely employed, few mucosal lesions should be missed on cytologic examination.

Endoscopy: Endoscopic examination was also quite valuable. As indicated in table 5, few examinations (9%) fail to disclose the lesion. However, the biopsy results were far less reliable. In almost half the cases the

TABLE 5

Endoscopy (34 Cases)

	Number	Positive*	Negative*	Biopsies		
				No. taken	+ for Ca	− for Ca
Gastroscopy	7	5	2	1	1	0
Esophagoscopy	27	26	1	24	13	11
Total	34	31	3	25	14	11

* Considered positive if any lesion seen; considered negative only if appeared absolutely normal.

biopsy report was negative for carcinoma. Hence the biopsy report cannot be given much weight, and the mere identification of a lesion is of greater significance. The percentage of positive endoscopic examinations is similarly high for all gastric carcinomas.[2, 3] However, although a lesion is frequently seen, the actual diagnosis often cannot be made from the visual or biopsy findings.

TABLE 6

Diagnostic Accuracy of X-Ray Study of Carcinoma of Stomach

Result	Entire Stomach		Proximal Third of Stomach		Distal Two Thirds of Stomach	
	No.	%	No.	%	No.	%
Correct diagnosis	217	80	45	72	172	83
Lesion seen but misdiagnosed	40	16	9	15	31	15
Lesion missed	12	4	8	13	4	2
Total	269	100	62	100	207	100

Radiography: In 62 of the 74 cases, gastrointestinal x-ray examinations were performed at The New York Hospital. The findings of these examinations were the subject of a previous report.[1] Table 6, reproduced from that report, shows that the diagnostic accuracy is substantially less when the lesion is confined to the proximal one third of the stomach than when the distal two thirds of the stomach is involved. In both series the incidence of misdiagnosis (lesion seen but not specifically identified as carcinoma) was 15%. However, the lesion was completely overlooked 13% of

the time when located in the proximal portion of the stomach. This occurred in only 2% of the cases showing distal involvement.

The conditions associated with inaccuracy of diagnosis and the value of specialized technics of radiographic examination were reported in detail.[1] However, certain conclusions should be emphasized. First, radiographic examination has certain limitations, particularly when the lesion is located in the proximal portion of the stomach. Repeated negative routine examinations do not conclusively rule out the presence of a lesion. Special technics of examination may improve diagnostic accuracy. Second, the x-ray report should specifically mention the possibility of malignancy in any lesion where benignity is in doubt.

Pathology: The findings of pathologic examination, either on the operating table or at autopsy, are summarized in table 7. The tumor was confined to the stomach in only four of the total series of 74 cases (5%). This contrasts with carcinoma in all parts of the stomach, where 22% of the tumors were apparently confined to the stomach.[3] In 13 cases there was spread to a single site, usually either distal esophagus or regional lymph nodes; in 57 cases multiple sites were involved. These observations, of course, represent only minimal spread of the tumor, determined at the time the definitive diagnosis was established. Undoubtedly, many foci were overlooked or not reported. The conclusion seems warranted that the tumor was rarely confined to the stomach. It was noted that patients with the longest duration of symptoms prior to diagnosis had the greatest spread beyond the stomach, with multiple sites of metastasis. However, even those diagnosed within one month of the onset of symptoms were likely to show multiple areas of spread. Of the four cases where the carcinoma was confined to the stomach, only one had symptoms of less than one month's duration.

TABLE 7

Organ Involvement by Carcinoma

Organ	All Cases	Cases with Single Area of Spread*
Proximal third stomach	74	
Regional nodes	44	4
Distal esophagus	43	6
Liver	25	0
Mesentery or omentum	23	1
Pancreas	19	2
Other intra-abdominal organs†	18	0
Other extra-abdominal organs‡	10	0
		Total 13

* Four cases showed no spread beyond stomach.
† Spleen, colon, diaphragm, adrenal, kidney.
‡ Heart, lung, pleura, pericardium, vertebra, rectal shelf, mediastinum.

Surgery and Survival: The operative procedures performed and the overall survival figures are detailed in table 8. Of the 61 operated patients who

were followed for at least one month after the operation, only six were living at last report. All six had been followed post-operatively for over 30 months. Four of the six had been followed for more than four years post-operatively, and two of these for over six years. Of the entire series of 74 cases, the known survivors represent only about 8%.

There are 51 operated patients who survived the operation and the immediate postoperative period (arbitrarily set at one month), and who were not lost to follow-up. The six living cases constitute 12% of this group. However, not all of these necessarily represent five-year survivals after operation. Thirty-nine of this latter group were operated upon with the possible hope of a cure (partial or total gastrectomies); the six survivors represent about 15% of this select group. Comparison with all gastric carci-

TABLE 8

Operations Performed and Postoperative Survival

	Total	Exploratory Laparotomy	Partial Gastrectomy	Total Gastrectomy
No follow-up	4	2	2	0
Died	55	16	31	8
Within 1 month	10	4	4	2
1–11 months	25	10	10	5
12–23 months	13	2	10	1
24–36 months	7	0	7	0
Living*	6	0	5	1
Total operations	65	18	38	9
Autopsy diagnosis	9			
Total in series	74			

* Living when last reported, at least 30 months postoperatively (30, 34, 48, 54, 74 and 97 months).

nomas shows that five-year survival in resected cases varies from 7% to 40%.[2, 4, 10, 11] If all patients, resected or not, are included, the five-year survival drops to from 2 to 15%.[2, 4, 10]

The number of cases of partial and total gastrectomy is too small to warrant any comparison. However, the results of partial gastrectomy appear to be at least as good as those of total gastrectomy in this series.

Factors in Postoperative Survival: The final tables (9 and 10) summarize the relationship of postoperative survival to various clinical findings and to the extent of spread of the tumor. The cases considered are the 51 who survived and were followed for at least one month after operation.

There is no relationship of survival to sex. However, patients in the middle age range of 50 to 69 years did significantly better than those in either the younger or the older age groups. Survival was very brief when the first symptom was other than pain or dysphagia. There was no remarkable difference between the latter two groups. Duration of symptoms prior to operation was apparently of no significance.

Patients with weight loss of at least 10 pounds appear to do better than

TABLE 9

Relationship of Clinical Features and Postoperative Survival (51 Cases*)

	Number Months Postoperative	Total	Sex		Age at Operation			First Symptom			Duration Symptoms (Months)		Weight Loss		Anemia		Gastric Acidity‡	
			Male	Female	Under 50	50 to 69	70+	Pain	Dysphagia	Other†	6 or less	More than 6	0 to 10 lbs.	Over 10 lbs.	Present	Absent	Absent	Present
Died	1–11	25	16	9	6	10	9	14	4	7	14	11	6	19	14	11	8	4
	12–23	13	9	4	2	10	1	7	4	2	10	3	2	11	4	9	5	2
	24–36	7	5	2	0	6	1	4	2	1	3	4	3	4	4	3	1	3
Living	30+	6	5	1	0	6	0	4	2	0	4	2	0	6	2	4	4	0
Total		51	35	16	8	32	11	29	12	10	31	20	11	40	24	27	18	9

* All cases who survived and were followed at least one month after operation.
† Flatulence, weakness, hematemesis, vomiting, anemia or regurgitation.
‡ Determined in 27 cases.

those with little or no weight loss. All the living patients belong to the former group. The presence or absence of anemia shows no relationship to survival. No valid conclusion can be reached regarding the relationship of gastric acidity to survival, although all living cases had zero free acid. It is worthy of emphasis that the living cases showed greater loss of weight and no free acid. However, the number of cases in the series is too small to warrant a definite conclusion.

In table 10 we have summarized the relationship of spread of the tumor to postoperative survival. In only one case of this selected group of 51 was the tumor confined to the stomach; this case was one of the six surviving patients. Except for one case with liver involvement, all cases with spread

TABLE 10

Relationship of Spread of Tumor to Postoperative Survival (51 Cases*)

	Number of Months	Total	Liver		Nodes		Esophagus		Other Intra-abdominal Organs†		Other Extra-abdominal Organs‡		No Spread
			+	−	+	−	+	−	+	−	+	−	
Dead	1–11	25	12	13	17	8	14	11	13	12	5	20	0
	12–23	13	3	10	9	4	9	4	7	6	1	12	0
	24–36	7	0	7	5	2	6	1	3	4	0	7	0
Living	30+	6	1	5	3	3	3	3	3	3	0	6	1§
Total		51	16	35	34	17	32	19	26	25	6	45	1

* All cases who survived and were followed at least 1 month after operation.
† Mesentery, omentum, pancreas, spleen, diaphragm, colon, kidney, adrenal.
‡ Pleura, lung, heart, mediastinum, rectal shelf.
§ Survived at least 97 months after operation.
+ indicates involvement by carcinoma; − indicates no involvement.

to the liver or to sites outside the abdomen had a very brief postoperative survival. Spread to the esophagus, the regional nodes or other intra-abdominal sites (except the liver) showed no definite correlation with survival. Five of the six surviving patients had spread to esophagus, regional lymph nodes or intra-abdominal organs.

Summary and Conclusions

1. Clinical observations in 74 patients with adenocarcinoma confined to the proximal third of the stomach are tabulated.

2. Although the two youngest patients were women, males predominated three-to-one. Most of the patients were over 50 years of age.

3. Pain and dysphagia were the predominant first symptoms and were rarely simultaneously absent. However, three patients were entirely asymptomatic. Weight loss was common. A palpable mass was detected in only 11% of the patients.

4. Laboratory studies showed that anemia was present in about half the cases. Occult blood was usually found in the stool but was not necessarily related to the anemia. Achlorhydria was present in about two thirds of the cases. Cytologic (Papanicolaou) study is of great aid in diagnosis.

5. Endoscopic examination was usually positive in disclosing a lesion, but biopsy results were often misleading.

6. Radiographic examination is of great aid in diagnosis of carcinoma of the stomach but has definite limitations for carcinomas limited to the proximal third.

7. Rarely (5%) was the carcinoma confined to the stomach. The longer duration of symptoms was associated with greater spread. However, widespread involvement was often seen in patients with very brief duration of symptoms.

8. Sixty-five of the 74 patients were operated upon, and resection was performed in 47 patients. The over-all survival (30 to 97 months) at the present time is 8%. These patients represent 15% of the resected group.

9. Severe weight loss, anemia, achlorhydria or local spread of the tumor was not associated with brief survival. Thus these findings should not rule out surgical intervention, with the hope of achieving prolonged survival and a possible "cure."

10. No favorable prognostic signs were determined. Short duration of symptoms and more radical operative procedures have not been associated with longer survivals.

Summario in Interlingua

Lesiones carcinomatose in le tertio proximal del stomacho presenta certe characteristicas que differentia los ab lesiones de location plus distal. Observationes clinic in 74 patientes con adenocarcinoma restringite al tertio proximal del stomacho esseva tabulate. Le datos assi obtenite esseva comparate con reportos in le litteratura medical concernite con casos de lesiones in altere portiones del stomacho.

Le duo plus juvene patientes in nostre serie esseva feminas, sed pro le total, masculos predominava in un proportion de tres a un. Le majoritate del patientes habeva plus que 50 annos de etate. Dolores e dysphagia esseva le predominante symptomas initial. Lor absentia esseva rar. Tamen, tres patientes esseva completemente asymptomatic. Perdita de peso esseva commun. Un massa palpabile esseva detegite in solmente 11% del patientes.

Studios laboratorial revelava que anemia esseva presente in circa un medietate del casos. Sanguine occulte esseva usualmente constatate in le feces. Illo non esseva necessarimente relationate a anemia. Achlorhydria se trovava in circa duo tertios del casos. Studios cytologic (Papanicolaou) es de grande valor in le diagnose. Le examine endoscopic esseva usualmente positive in le revelation del lesion, sed le resultatos de biopsia esseva frequentemente deceptive. Le examine radiographic es de grande valor in le diagnose de carcinoma del stomacho, sed illo ha stricte limitationes in le caso de carcinomas restringite al tertio proximal.

Le restriction del carcinoma al stomacho esseva rar (5%). Presentia prolongate del symptomas esseva associate con dissemination del lesiones. Tamen, extense affectiones esseva notate frequentemente in patientes con symptomas de breve duration.

Sexanta-cinque del 74 patientes esseva operate. Resection esseva effectuate in 47 casos. Al tempore presente le superviventia (30 a 97 menses) amonta a 8% del gruppo total. Le superviventes constitue 15% del gruppo resectionate. Sever perdita de peso, anemia, achlorhydria, o diffusion local del tumor non esseva associate con breve intervallos de superviventia. Ergo le presentia de iste factores non justifica abandonar le spero de effectuar un superviventia prolongate e possibilemente un "cura" per medio del intervention chirurgic. Del altere latere, nulle favorabile signos prognostic esseva determinate. Breve duration del symptomas e plus radical manovras chirurgic non esseva associate con prolongation del superviventia.

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CHOLECYSTOGRAPHY IN THE PRESENCE OF JAUNDICE *

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The diagnosis of the specific disease in which jaundice is the presenting symptom has been surprisingly accurate in an impressive majority of instances. In the remaining small percentage without an apparent diagnosis, extremely difficult problems may be encountered. Following a detailed history and thorough physical examination alone, a correct diagnosis should be made in 80 to 85% of patients in whom jaundice is one of the major complaints.[11] This may be aided by the knowledge that about 50% of cases with jaundice are of the obstructive type. Despite the inferential assistance provided by statistical data, liver function studies and liver biopsy, the balance of these problem cases may continue to evade a satisfactory or definitive solution. The tendency to place unquestioning dependency on patterns of laboratory tests and also on histologic reports can lead to confusion and error. For example, these accepted criteria may point toward a diagnosis compatible with obstructive jaundice, but may fail to differentiate between the extrahepatic or intrahepatic origin of the pathology. One of the important aids in the study of biliary tract disease has been provided by the x-ray examination. In the absence of jaundice, its index of accuracy is very high. With jaundice, its usefulness and reliability have been limited.

Earlier reports have been published on gall-bladder visualization in jaundiced patients. Rudisill [8] found that a visualized gall-bladder was obtained in seven of eight patients in whom a diagnosis of catarrhal jaundice had been made. Foley [6] reported a normal cholecystogram in 68% of patients with jaundice due to intrahepatic disease, and complete failure to obtain a gall-bladder shadow in 13 cases of "surgical jaundice." Nord [5] observed that as jaundice becomes more pronounced the degree of adequate cholecystographic visualization decreased. As the degree of hyperbilirubinemia receded there was improvement in the visualization of the gall-bladder. Foote and Carr [1] pointed out that, in the presence of jaundice, opacification of the gall-bladder sometimes required up to 24 hours. They attempted to differentiate parenchymatous from obstructive jaundice by the promptness with which the gall-bladder emptied following a fatty meal, claiming that delay in emptying was due to interference in the flow of bile through the extrahepatic biliary passages. Others have failed to verify these observations. Huber [2] likewise reported that, in 11 of 15 cases of obstructive jaundice, a gall-bladder shadow

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failed to appear, but in hepatocellular jaundice good visualization was obtained in seven of 10 patients studied. A uniform observation of these earlier reports was the absence of toxic effects following the administration of the opacifying medium.

This study was undertaken to determine the feasibility of roentgen examination of the biliary tract in the presence of jaundice, to determine under what circumstances the most desirable results could best be obtained, and to investigate the relative merits of the newer oral and parenteral materials employed for opacification of the gall-bladder and its ductal system.

Method of Study

This group of cases consisted of patients who were unselected except for the presence of jaundice. An attempt was made to visualize the biliary tract by the intravenous method employing iodipamide, and as a separate procedure by iopanoic acid tablets through the more conventional oral route. After the usual precautionary measures were exercised, a single dose of 20 c.c. of 52% iodipamide was administered according to accepted technic. Roentgenograms of the common duct were taken at 15- to 30-minute intervals, and of the gall-bladder one to two hours later. The procedure was not repeated when opacification was not observed. If nonvisualization of the gall-bladder resulted after the ingestion of six tablets of iopanoic acid, the reëxamination was ordered in 24 hours following another dose of the dye. The serum bilirubin value was obtained in a great majority of patients within 24 to 48 hours of the roentgen examination, and the interval never exceeded a three-day span. The diagnosis in each case was established by surgery, by liver biopsy or by careful clinical evaluation.

Results

A total of 50 cases of jaundice was studied. The jaundice was classified according to the diagnoses of acute hepatitis, cirrhosis, liver metastases, obstruction and hemolytic disease. Cases of obstructive jaundice included stone in the common duct, carcinoma of the head of the pancreas, duodenal diverticulum occluding the common duct, metastatic nodes producing extrinsic pressure on the common duct, and edema of the biliary channels associated with attacks of acute cholecystitis. Despite the clinical picture characteristic of obstructive jaundice, cases in which the pathology occurred primarily within the confines of the liver, such as Thorazine hepatitis or cholangiolitic disease, were considered to be intrahepatic disorders requiring nonsurgical management.

Of the 50 patients examined with iodipamide, a visualized gall-bladder was demonstrated in 21 instances, or 42%. If the series is divided into cases where the serum bilirubin is more than, or less than, 5.0 mg. %, disproportionate values are obtained. Eighteen patients, encompassing all types of jaundice, and in whom the serum bilirubin was greater than 5.0

mg. %, were examined and the gall-bladder was visualized in three, or about 17%. Of the eight cases of obstructive jaundice in the more severe degree of hyperbilirubinemia, two satisfactory gall-bladder examinations were obtained. Likewise, where the degree of icterus was more intense, only one of six cases of hepatitis revealed a normal gall-bladder. Among the 32 patients having serum bilirubin values of less than 5.0 mg. %, gall-bladder opacification was obtained in 18 cases, or about 56%. In this same category, 10 gall-bladders (45%) of the 22 cases of obstructive jaundice could be visualized, while in the group of hepatitis, all the six cases demonstrated an opacified viscus. The one case of cirrhosis in the higher bilirubin level

TABLE 1

Jaundice

		Obstruction	Hepatitis	Cirrhosis	Metastases	Hemolytic	Total
Total Cases Studied		8	6	1	3	0	18
Serum Bilirubin above 5.1 mg. %	G.B. visualized by Iodipamide	2	1	0	0		3
	Iopanoic acid	1	1	0	0		2
	C.D. visualized by Iodipamide	1	0	0	0		1
	Iopanoic acid	0	0	0	0		0
Total Cases Studied		22	6	2	1	1	32
Serum Bilirubin below 5.0 mg. %	G.B. visualized by Iodipamide	10	6	1	0	1	18
	Iopanoic acid	2	3	0	0	1	6
	C.D. visualized by Iodipamide	15	4	0	0	1	20
	Iopanoic acid	1	1	0	0	1	3

G.B. = gall-bladder.
C.D. = common duct.
Iodipamide = Cholografin.
Iopanoic acid = Telepaque.

failed to produce a visualized gall-bladder, and of the two cases in the lower range of bilirubinemia a positive cholecystogram could be obtained in only one. A gall-bladder shadow failed to appear in all cases of jaundice associated with liver metastases, regardless of the degree of icterus. The single patient in whom hemolytic jaundice was diagnosed demonstrated a normally visualized gall-bladder when the bilirubinemia was 1.4 mg. %.

A total of 12 cholecystograms was seen in patients with obstructive jaundice. Cholelithiasis was observed in 10 cases of this group. In the remaining two instances a visualized gall-bladder without stones was reported, and at surgery the obstruction to the flow of bile was found to be due to a pancreatic carcinoma in one case and, in the other, a duodenal diverticulum exerting pressure against the opening of the common duct. In the seven

cases of hepatitis in which the gall-bladder concentrated the opaque medium a normal cholecystogram was obtained, and this finding was true also in each single case of jaundice due to hemolytic disease and cirrhosis.

During the course of this study an attempt was made to visualize the common duct, but the examination was not carried out in all instances with benefit of specialized technics such as planigraphy or the constricting effect of the terminal portion of the common duct frequently evoked by morphine. Outline of the common duct was demonstrated in 20 (40%) of the 50 cases studied. The duct was not visualized in the presence of a severe degree of jaundice. In the lower levels of bilirubinemia the duct was seen in 15 of 22 cases (68%) of obstructive jaundice, and in four of six cases of infectious hepatitis. A stone was detected in the common duct in two cases of obstructive jaundice, a finding which was verified in the one case which came to surgery. In six additional common duct explorations, stones were found in five patients and debris in one. X-ray examination had failed to demonstrate these abnormalities.

Comparison was made between the relative effectiveness of iodipamide and iopanoic acid in regard to satisfactory visualization of the gall-bladder. There was a total of 21 cases in which iodipamide and iopanoic acid were each used in the same patient. Iodipamide provided satisfactory opacification of 13 gall-bladders, and seven were opacified with iopanoic acid. In obstructive jaundice a cholecystographic study was obtained in eight cases following the use of the intravenous medium, and in three cases in which iopanoic acid was employed. A normal gall-bladder was reported in three cases of infectious hepatitis studied with iodipamide, and in two cases following administration of iopanoic acid.

Roentgen findings were compared with operative findings when both were obtainable in the same patient. In a group of eight patients whose serum bilirubin was above 5.0 mg. % not one gall-bladder was visualized. The surgical diagnoses were cholelithiasis (four), carcinoma of the pancreas (two), and hepatic metastases (two). There were 11 patients in the group of less intense icterus in whom x-ray and operative results were compared. Cholelithiasis was demonstrated roentgenographically in five patients and corroborated by surgical exploration. In six cases of a nonvisualized gall-bladder, stones were found in the gall-bladder in each instance at operation.

No unfavorable effects were experienced by any patient in this survey by the administration of either iodipamide or iopanoic acid in the presence of jaundice. On a clinical basis, it did not appear that the course of the disease in any patient was altered, nor was convalescence impeded following the use of either of these radiopaque substances.

Comment

The most reliable assistance that can be expected from x-ray examination of the biliary tract in the presence of jaundice will be derived by such posi-

tive findings as a visualized gall-bladder and/or common duct. In this study each roentgen diagnosis of cholelithiasis was corroborated by the finding of stones at operation. The unequivocal demonstration of gall-bladder stones therefore becomes a very important aid in establishing a diagnosis of cholecystitis and cholelithiasis as the most probable basis of jaundice. A normally visualized gall-bladder without stones invariably was reported in infectious hepatitis within the appropriate bilirubin ranges. A reasonable conclusion may be reached, therefore, that in the finding of an opacified viscus without intrinsic abnormalities there is little likelihood of gall-bladder disease's contributing to jaundice which may be due to other causes. In two cases a satisfactorily visualized gall-bladder was checked at surgery, and common duct obstruction was found to be due to a duodenal diverticulum in one and to pancreatic carcinoma in the other. The ability to obtain a normally visualized gall-bladder without stones should not be considered sole reason to decide arbitrarily against a diagnosis of obstruction as cause for the jaundice.

Failure to obtain a cholecystogram in the presence of jaundice is less helpful toward establishing a diagnosis of the underlying mechanism. Factors contributing to nonvisualization of the gall-bladder, such as the height of the bilirubinemia, degree of liver damage, and existence of chronic cholecystitis, comprised too many variables to obtain conclusive information from a negative cholecystographic report. It is suggested, therefore, that other diagnostic criteria be employed under conditions of a negative gall-bladder x-ray in an effort to classify the type of jaundice.

The lack of close correlation between routine x-ray examination and surgical finding of common duct stone supports the impression that x-ray examination of the common duct in the presence of jaundice has limited value. Whether greater accuracy might have been obtained with more detailed x-ray technics must await further study. Moreover, the common duct could not be visualized in close to 50% of the patients who were icteric.

According to results obtained when iodipamide and iopanoic acid were employed, the intravenous method appears to be more effective in opacifying the biliary tract when jaundice exists.

Conclusions

1. Cholecystography in the presence of jaundice is a feasible and helpful procedure in the diagnosis of biliary tract disease.

2. The results of the x-ray examination of patients presenting jaundice should be interpreted with the proper understanding of certain recognized limitations.

3. The benefits of x-ray examination of the gall-bladder and/or common duct in the presence of jaundice are best derived through positive findings. A normally visualized gall-bladder without stones strongly points to intrahepatic disease as the basis of the jaundice. However, extrahepatic and

extrabiliary obstructive phenomena should not be ruled out as a cause of jaundice by such a normal report.

4. The percentage of positive findings is likely to be higher if the examination is performed in patients whose serum bilirubin level is less than 5.0 mg. %.

5. Administration of the radiopaque substances appeared to have no untoward effect on the patients, nor did it interfere with the course of the disease.

SUMMARIO IN INTERLINGUA

Le presente studio esseva interprendite pro determinar le practicabilitate de examines roentgenographic del vias biliari in le presentia de jalnessa, pro establir le conditiones sub le quales le melior resultatos pote esser obtenite, e pro investigar le meritos relative del plus recente materiales oral e parenteral pro le opacification del vesica biliari e su systema de ductos. Esseva interprendite le tentativa de visualisar le vias biliari per medio del technica intravenose. In isto iodipamido (Cholografino) esseva usate. In un manovra separate, acido iopanoic (Telepaque) in forma de tablettas esseva administrate conventionalmente per via oral. Inter le 50 patientes examinate con iodipamido, le vesica biliari se provava visualisabile in 21 casos (42%). Dece-nove patientes con omne typos de jalnessa e con nivellos de bilirubina de plus que 5,0 mg pro cento esseva examinate. Le vesica biliari esseva visualisate in duo casos (12%). Inter le 32 patientes con valores seral de bilirubina de infra 5,0 mg pro cento, le vesica biliari se monstrava opacificate in 19 casos (circa 59%). Le gruppo de casos con le plus sever grados de hyperbilirubinemia includeva nove casos de jalnessa obstructive. Inter istos, un sol satisfacente examine del vesica biliari esseva effectuate. Similemente, inter sex casos de hepatitis, un sol normal vesica biliari esseva reportate. Del altere latere, in le casos in que le nivellos seral de bilirubina esseva minus que 5,0 mg pro cento, il esseva constatate que un medietate del vesicas biliari del 22 patientes con jalnessa obstructive poteva esser visualisate, e in le gruppo del patientes con hepatitis, omne le sex casos exhibiva un viscere opacificate. Un total de 12 cholecystogrammas esseva vidite in patientes con jalnessa obstructive. Cholelithiasis esseva constatate in 10 casos in iste gruppo. In le septe casos de hepatitis in que le vesica biliari effectuava un concentration del medio de opacification, un normal cholecystogramma esseva obtenite. Esseva executate un comparation inter iodipamido e acido iopanoic con respecto a lor efficacia relative in effectuar un visualisation satisfactori del vesica biliari. In un serie de 21 casos, iodipamido e acido iopanoic esseva usate ambes in le mesme patiente. Iodipamido effectuava un satisfacente grado de opacification de 13 vesicas biliari. Septe vesicas biliari esseva opacificate satisfacentemente per medio de acido iopanoic. In jalnessa obstructive, le studio cholecystographic poteva esser effectuate in octo casos per medio del substantia intravenose e in tres casos per medio de acido iopanoic. Un normal vesica biliari esseva reportate in tres casos de hepatitis infectiose studiate per medio de iopamido e in duo casos studiate per medio de acido iopanoic. Nulle effectos adverse esseva experientiate per ulle patiente in iste studio in consequentia del administration de o iodipamido o acido iopanoic in le presentia de jalnessa. Nihil pareva indicar que le curso del morbo in ulle del patientes esseva alterate o que le convalescentia esseva retardate per le uso del un o del alter del duo substantias de radio-opacification.

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POLYCYTHEMIA OF OBESITY: FURTHER STUDIES OF ITS MECHANISM AND A REPORT OF TWO ADDITIONAL CASES *

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A RELATIONSHIP between polycythemia and obesity became apparent to us during observation of a massively obese patient who had serious renal, hepatic and cardiorespiratory disturbances, as well as marked polycythemia. Polycythemia and the other disturbances were remarkably reversed in this patient by dietary weight reduction without any other therapy.[1, 2] Baez Villaseñor and his co-workers [3] had previously described a 5% incidence of polycythemia in a group of 240 obese patients studied in Mexico. Incidental reference to the presence of obesity in cases of atypical erythremia and the observation of unusual plethora in obese individuals were made by several other authors.[4-6] An analysis of the frequency with which polycythemia occurred in obese individuals studied at the University of Minnesota revealed that polycythemia was 10 times more frequent in the pathologically obese than in the unselected hospital population.[2]

In an earlier paper,[2] three cases of polycythemia associated with obesity were reported and the existence of a distinct syndrome was proposed, referred to as "polycythemia of obesity." At approximately the same time, two other groups of investigators independently indicated the existence of such an entity. Auchincloss, Cook and Renzetti [7] studied one patient and cited the two additional cases which Newman, Feltman and Devlin [5] had described as unusual cases of polycythemia vera in obese individuals. In each of these the hematologic findings were not typical of polycythemia vera, and the existence of arterial hypoxemia and carbon dioxide retention was noted. Sieker and co-workers [8] studied four patients who displayed extreme obesity, polycythemia and other physiologic abnormalities very similar to those observed by the other authors. Two additional patients with the same syndrome have recently been studied at the University of Minnesota, and these will be described below.

Since polycythemia of obesity completely subsides with reversal of obesity, it is of considerable practical importance to distinguish it from polycythemias due to other causes not susceptible to such simple and safe therapy. Five cases of polycythemia of this type were recognized at this

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center within a period of only two years, and each of these had previously been diagnosed as polycythemia vera. This has suggested that this condition is not at all rare and that many unrecognized cases exist.

Case Reports

Case 1. The patient, a 45 year old married bartender, was admitted to the Minneapolis Veterans Administration Hospital on October 21, 1954, complaining of progressive shortness of breath, ankle edema and nocturia. Obesity had been present since early adulthood, but his weight had increased from 230 to 360 pounds between 1951 and 1954. The dietary history indicated a markedly excessive food intake, supplemented by large quantities of alcohol. He had been hospitalized on two occasions in the preceding year for treatment of congestive heart failure.

On admission the patient displayed moderate dyspnea at rest. He was 5 feet 9 inches tall (175.3 cm.) and weighed 306 pounds (138.9 Kg.). Xanthomata were present on both upper eyelids, and the head and neck areas were plethoric. Lips and fingernails were mildly cyanotic. Moist râles were heard on inspiration in both lung bases. The heart was not enlarged. A moderate amount of edema and also stasis dermatitis were present in both legs.

Initial laboratory examination revealed a hemoglobin of 18.0 gm. and hematocrit of 58%. The red blood cell count was 5,820,000 per cubic millimeter, the white count was 5,600 cells per cubic millimeter, and the differential count was essentially normal. The platelet count was 189,000 per cubic millimeter, eosinophil count was 222 cells per cubic millimeter, and reticulocytes were 1.8%. The mean corpuscular volume was 118 cubic microns; mean corpuscular hemoglobin concentration, 36.5 micromicrograms, and mean corpuscular hemoglobin concentration, 32%. Bone marrow smear and biopsy revealed mild normoblastic hyperplasia and occasional lipid histiocytes. Routine urinalysis, blood urea nitrogen concentration and urine concentration and dye excretion tests were all within normal limits. Serum uric acid was elevated to 9.1 mg.%. Serum direct reacting and total bilirubin were normal, but bromsulphalein retention (at 45 minutes) was 28.2%, and flocculation tests indicated moderate hepatocellular damage. The prothrombin time was 15.7 seconds (control, 12.5 seconds), but bleeding and clotting times were normal. Needle biopsy of the liver revealed changes indicative of moderately advanced portal cirrhosis. The carbon dioxide combining power was 35.4 mEq./L. (78.6 vol. %). The arterial oxygen saturation was 90.3% at rest, 96.2% during hyperventilation on air, and 100% while the patient was breathing oxygen. The total vital capacity was 2.4 L. X-ray and fluoroscopic examination of the chest revealed high diaphragms and normal heart size. Left axis deviation was noted on the electrocardiogram. The estimated total blood volume was 9,900 ml.*

The patient was placed on an 1,800-calorie diet, supplemented with brewer's yeast and multivitamins. Digitalis was continued during the first month of his hospital stay. He was kept under hospital observation for 76 days. With a progressive decrease in weight to 263 pounds (119.4 Kg.), the hemoglobin fell to 16.5 gm. and the hematocrit to 49.5%. The carbon dioxide combining power was reduced to 31 mEq./L. (68.8 vol. %) and the estimated total blood volume to 8,270 ml. The vital capacity was increased to 3.5 L. Liver function markedly improved.

Following discharge from the hospital on January 4, 1955, the patient abandoned the prescribed diet, and on August 9, 1955, he presented himself to the University Hospitals complaining of distressing dyspnea on mild exertion. His weight had

* The total blood volume in both of the present cases was measured with radioactive chromium (Cr^{51}) labeling of red blood cells. A venous hematocrit correction of 0.86 was employed for estimation of the total blood volume.

increased to 294.5 pounds (133.7 Kg.). There was no evidence of heart failure. No change in the thoracic circumference measurements occurred between inspiration and expiration. The hemoglobin was 17.9 gm.%; hematocrit, 51.5%; CO_2 combining power, 29 mEq./L. (64.4 vol. %). The vital capacity was 2.4 L. Arterial oxygen saturation at rest was 90.6%; during hyperventilation on air, 92.0%; upon breathing pure oxygen, 100%. On an 800-calorie diet, the patient's weight was reduced to 277 pounds (125.8 Kg.) over a period of three weeks, with excellent subjective improvement, but the patient failed to return for subsequent laboratory studies.

Case 2. The patient, a 68 year old housewife. was admitted to the University Hospitals on June 3, 1955, because of dyspnea and orthopnea. Ten years earlier she had weighed 270 pounds (122.6 Kg.), and her blood pressure was said to have been significantly elevated. Marked obesity persisted, and during the four years preceding her admission, cyanosis of the face and lips had appeared. An episode of congestive heart failure had occurred three weeks prior to hospitalization, with minimal improvement following digitalization, diet and weight reduction. On the basis of a venous hematocrit of 65%, polycythemia vera was tentatively diagnosed. In spite of venesections totaling 1,200 ml., dyspnea, cyanosis and polycythemia persisted.

The patient was acutely dyspneic on admission. Her lips and fingernails were strikingly cyanotic. She was 5 feet 4 inches (162.6 cm.) tall and weighed 229 pounds (104.0 Kg.). The blood pressure was 210/104 mm. Hg, and the pulse was irregular at a rate of 76 beats per minute. Retinal veins were engorged. The chest circumference at the level of the third intercostal space was 100 cm., and less than a 1 cm. change occurred between maximal inspiration and expiration. Examination of the lungs was not remarkable. The apical impulse was displaced to the anterior axillary line at the level of the sixth intercostal space. Edema of the lower extremities was graded 2 plus.

On admission, laboratory study revealed a hemoglobin of 18.6 gm. and a hematocrit of 60.5%. The red blood cell count was 6,400,000 per cubic millimeter; differential count, 65% neutrophils, 2% neutrophilic myelocytes, 29% lymphocytes, 2% monocytes and 2% basophils. Platelet count was 150,000 per cubic millimeter; reticulocytes, 1.8%. The mean corpuscular volume was 101 cubic microns; mean corpuscular hemoglobin, 25 micromicrograms; mean corpuscular hemoglobin concentration, 31%. Bone marrow smear and aspiration biopsy showed mild normoblastic hyperplasia. Routine urinalysis was negative. The blood urea nitrogen was 35 mg.%; creatinine, 2.6 mg.%. Bromsulphalein retention was 16% at one-half hour, but other liver function studies and the serum cholesterol values were unremarkable. The carbon dioxide combining power was 37 mEq./L. (82.1 vol. %), but other serum electrolytes, including sodium, potassium and chloride, were normal, and the urinary 17-hydroxycorticoid excretion was likewise normal. Arterial oxygen saturation at rest was 63% on room air and 100% while the patient was breathing 100% oxygen. The vital capacity was 1.0 L. (0.9 L. at one second). X-ray and fluoroscopic examination of the chest revealed mild generalized cardiac enlargement and prominent pulmonary vascular markings. The electrocardiogram showed a nodal rhythm and ST and T changes probably related to digitalis therapy. The estimated blood volume was 6,400 ml.

Hospital observation was continued for a period of 70 days and the patient was most coöperative, particularly with adherence to an 800-calorie, low sodium diet. Digitalis was discontinued soon after admission. Continuous and, later, intermittent oxygen was required during the first three weeks for relief of episodes of dyspnea with marked cyanosis. A trial dose of 5 mg. of morphine sulfate administered subcutaneously on the sixth hospital day caused the patient to lapse into a stupor with Cheyne-Stokes respiration. Two phlebotomies were performed during the second week of hospitalization, with removal of a total of 1,100 ml. of blood. No other therapy was used.

With weight reduction, dyspnea subsided and polycythemia was gradually reversed (figure 1). At the time of discharge on July 30, 1955, the weight had been reduced to 194 pounds (88.1 Kg.), hemoglobin to 15.3 gm.%, and hematocrit to 47%. The vital capacity had increased to 2.0 L. (1.7 L. in one second), and the arterial oxygen saturation when the patient was breathing room air had increased to 78.6%. Dyspnea and cyanosis at rest had disappeared.

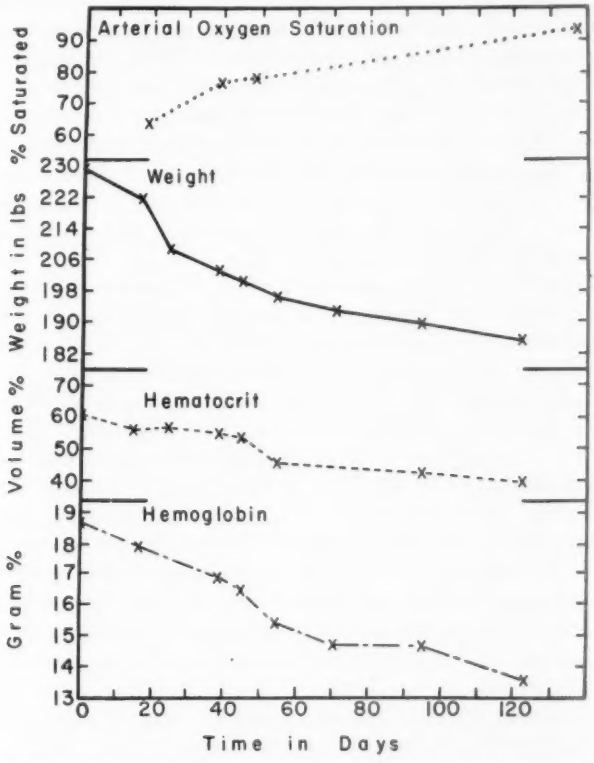

FIG. 1. *Case 2.* Relationship of the hemoglobin, hematocrit and arterial oxygen saturation values to weight loss.

Three months after discharge the patient reported that she felt well and tolerated moderate activity without dyspnea. Her weight was 193 pounds (87.6 Kg.); hemoglobin, 12.9 gm.%; hematocrit, 40%; vital capacity, 2.3 L. (2 L. in one second). The arterial oxygen saturation when she was breathing room air had increased to 93.5% and the CO_2 combining power had fallen to 30 mEq./L. (66.6 vol. %). The estimated total blood volume was 6,115 ml.

DISCUSSION

Polycythemia of obesity is a form of secondary polycythemia which occurs in patients with extreme obesity. Contrary to our earlier impression, arterial oxygen saturation may be only slightly reduced (case 1), or may

be markedly depressed (case 2). Exercise and short periods of breath holding produce a prompt fall in the arterial oxygen saturation.[8] Cyanosis occurred in six of the 12 collected cases and was a prominent feature in the second case reported above. Most of the patients initially consulted a physician because of dyspnea, and congestive heart failure was present in a majority of the reported cases.

In this syndrome the hematologic findings are limited to the erythroid elements. No change in the peripheral blood picture is found except for the increased number and perhaps increased size of the red blood cells. Unlike polycythemia vera, neither the white blood count nor the platelet count is elevated. Bone marrow study may reveal mild erythroid hyperplasia, but diffuse hyperplasia involving the myeloid and megakaryocytic series, characteristic of polycythemia vera, is not observed. The estimated total blood volume is slightly elevated, with a marked increase in red cell volume and a decrease in plasma volume.

Cyanosis and arterial anoxemia suggest a diagnosis of congenital heart disease with right-to-left shunt. However, the observation that full arterial oxygen saturation is promptly achieved while the patient is breathing 100% oxygen is significant evidence against the presence of a clinically important venous-arterial shunt. Precise measurements of physically dissolved oxygen may be necessary to detect shunts of small magnitude.[9] The presence of congestive heart failure in several patients was regarded as a further complication of polycythemia and severe obesity. Cardiac decompensation per se could not be implicated as a cause of the polycythemia.

It appears likely that the sequence of events leading to polycythemia is initiated by a reduction in alveolar ventilation. The thoracic cavity is crowded by fat from within and without, and the total lung volume is therefore decreased. These changes are related to a marked decrease in vital capacity. Sieker and co-workers [8] have noted that the expiratory reserve volume was decreased to as little as 17% of the normal value. With such severe curtailment of the volumes of air exchanged, alveolar ventilation becomes inadequate, at first during exercise and later at rest. Normal oxygenation of blood in the pulmonary capillaries cannot be maintained and the arterial oxygen saturation falls. Because insufficient quantities of inspired air are brought to the alveoli, carbon dioxide elimination is also impaired and the blood carbon dioxide concentration rises.

Clinically, these abnormalities are reflected in shallow breathing, Cheyne-Stokes respiration and cyanosis. The chest circumference may remain essentially unchanged between maximal inspiration and expiration. Normal breathing seems to require greatly increased effort, and the patients tend to be somnolent.

The principal physiologic abnormalities which we observed in four of our cases before and after weight reduction are indicated in the accompanying table. No attempt was made to improve respiration by training. It

will be noted that weight reduction was followed by a reversal of the syndrome, with a fall of the hemoglobin concentration, the venous hematocrit and the carbon dioxide combining power to near normal values. At the same time there was a corresponding increase in the vital capacity and arterial oxygen saturation values. We have postulated that the patients' improvement resulted from partial removal of the mechanical barrier to respiration created by fat, a decrease of the body's total metabolic requirement, and an increase in effectiveness of the respiratory musculature.

Since the ventilatory defect in these patients is closely related to the mechanical limitations imposed by massive obesity, this defect differs from an entity recently described by Comroe and co-workers,[9, 10] in which hypoventilation was attributed to dysfunction of the medullary respiratory center.

TABLE 1

Physiologic Changes in Patients with Polycythemia of Obesity before and after Weight Reduction

Patient	Weight lb.		Hemoglobin gm. %		Hematocrit vol. %		CO_2 Combining Power mEq./L.		Arterial O_2 Saturation %		Vital Capacity L.		Blood Volume ml.	
	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final	Initial	Final
(1)*	380	259	21.5	14.5	73	46	34.2	27.0	90.8	95.7	3.2	4.4	—	—
(2)*	305	276	21.0	16.0	54	48	—	34.0	—	95.5	—	3.3	—	8,000
(3)†	306	263	18.0	16.5	58	49.5	35.4	31.1	90.3	—	2.4	3.5	9,900	8,270
(4)‡	229	193	18.6	12.9	60.5	40.0	37.0	30.0	63	93.5	1.0	2.3	6,400	6,115

* Previously reported[2].
† Case 1.
‡ Case 2.

In contrast to our patients, Comroe's patient displayed no mechanical limitation of respiration, and the lung volumes were entirely normal. Three instances of polycythemia have recently been reported in association with large uterine myomas, with complete reversal of polycythemia after surgical removal of the fibroids.[11–13] It is possible that more detailed study of such cases will show that large abdominal tumors restrict respiratory movement and produce polycythemia by a mechanism similar to that in the patients with obesity. This may also apply to instances of polycythemia related to ascites.[14]

SUMMARY AND CONCLUSIONS

An increased incidence of polycythemia has previously been noted in obese patients. However, the existence of a distinct syndrome, referred to as "polycythemia of obesity," has only recently been recognized in independent reports from three medical centers. This condition is a form of secondary polycythemia closely related to the restriction of pulmonary ventilation imposed by massive obesity. In the present report, the essential features of this syndrome are analyzed and two new cases are described.

The condition is characterized by inadequate alveolar ventilation, resulting in arterial hypoxemia and carbon dioxide retention. The vital capacity is markedly reduced. Clinical features include a variable degree of cyanosis, shallow breathing, Cheyne-Stokes respiration and intermittent heart failure. The chest circumference may remain essentially unchanged between maximal inspiration and expiration. Normal breathing seems to require greatly increased effort, and the patients tend to be somnolent.

Unlike polycythemia vera, there is no consistent increase in immature cells, white blood cells or platelets accompanying the increase in red blood cells in the peripheral blood. The bone marrow examination may reveal mild erythroid hyperplasia, but diffuse hyperplasia involving the myeloid and megakaryocytic series, characteristic of polycythemia vera, is not observed. Cyanosis and arterial anoxemia suggest a diagnosis of congenital heart disease with right-to-left shunt. This may be excluded by the observation that full arterial oxygen saturation is promptly achieved while the patient is breathing 100% oxygen.

Weight reduction was followed by reversal of the syndrome, with a fall of the hemoglobin concentration, the venous hematocrit, and the carbon dioxide combining power to near-normal values. At the same time there was a corresponding increase in the vital capacity and arterial oxygen saturation values. We have postulated that the patients' improvement resulted from a partial removal of the mechanical barrier to respiration created by fat, a decrease of the body's total metabolic requirement, and an increase in effectiveness of the respiratory musculature.

This syndrome does not appear to be at all rare, and many unrecognized cases are thought to exist. Since the condition is promptly reversed by weight reduction without any other therapy, it has been of practical value to distinguish it from polycythemia due to other causes.

Acknowledgment

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Summario in Interlingua

Un augmento del incidentia de polycythemia ha previemente essite notate in patientes obese. Tamen, le existentia de un distincte syndrome, designate como "polycythemia de obesitate," ha essite recognoscite solmente recentemente in reportos independente ab tres centros medical. Le condition in question es un forma de polycythemia secundari, nettemente relationate al restriction del ventilation pulmonar que resulta de obesitate massive. In le presente reporto, le characteristicas essential de iste syndrome es analysate, e duo nove casos es describite.

Le condition se distingue per inadequate ventilation alveolar, con le resultato de hypoxemia arterial e retention de bioxydo de carbon. Le capacitate vital es marcatemente reducite. Le tractos clinic include variabile grados de cyanosis, un respiration pauco profunde, respiration de Cheyne-Stokes, e intermittente disfallimento cardiac. Le circumferentia thoracic pote remaner plus o minus incambiate inter

inspiration maximal e expiration maximal. Le respiration normal pare requirer un multo augmentate effortio, e le patientes tende a submerger se in un stato de somnolentia.

Per contrasto con polycythemia ver, il non ha in iste condition un regular augmento del cellulas immatur, del leucocytos, o del plachettas parallel al augmento del erythrocytos in le sanguine peripheric. Le examine del medulla ossee pote revelar leve grados de hyperplasia erythroide, sed le diffuse hyperplasia del series myeloide e megacaryocytic, que es un characteristica de polycythemia ver, non es incontrate. Le presentia de cyanosis e anoxemia arterial suggere un diagnose de congenite morbo cardiac con derivation dextero-sinistre. Iste possibilitate pote esser eliminate per le observation que complete saturation oxygenic del sanguine arterial es promptemente effectuate quando le patiente respira 100% de oxygeno.

Le reduction del peso esseva sequite per un reversion del syndrome, con redescendita a nivellos quasi normal del concentration de hemoglobina, del hematocrite venose, e del potentia de ligar bioxydo de carbon. Simultaneemente il occurreva un augmento correspondente del capacitate vital e del valores del saturation oxygenic arterial. Nos postula que le melioration del patiente resultava del partial ablation del obstruction mechanic del respiration representate per le grassia, del reduction del total requirimentos metabolic del corpore, e de un augmento del tono del musculatura respiratori.

Iste syndrome es apparentemente non rar del toto. Nos opina que il existe de illo multe non recognoscite casos. Proque le condition es promptemente revertite per reduction de peso sin ulle altere therapia, su distinction ab polycythemia effectuate per altere causas es de valor practic.

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STUDY OF C-REACTIVE PROTEIN IN THE SERA OF PATIENTS WITH ACUTE MYOCARDIAL INFARCTION *

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Classic myocardial infarction rarely presents a diagnostic problem; the history, physical findings, electrocardiographic changes and alteration of the erythrocyte sedimentation rate all clearly indicate the diagnosis. In states of coronary insufficiency where lesser degrees of myocardial necrosis supervene, the diagnosis often is not apparent, and newer diagnostic aids are therefore sought. One such newer aid, the C-reactive protein, is promising.

C-reactive protein, an abnormal protein absent from the blood of normal patients, appears as an acute phase response in a variety of clinical conditions, such as inflammation, neoplasia and granuloma formation.[1] Löfström,[2, 3] employing the technic of pneumococcus capsular swelling for detecting C-reactive protein in patients' sera, described the appearance of this abnormal protein following acute myocardial infarction. Hedlund,[4] utilizing the same method, studied the sera of 48 patients with myocardial infarction. All but one had C-reactive protein in their blood. The acute phase protein appeared on the second or third day, reached its maximum on the fourth day, and then gradually decreased. In another group of 11 patients with angina pectoris only, no abnormal protein was detected in the blood.[4] With the availability of the more sensitive method of detecting C-reactive protein in human blood, employing C-reactive protein rabbit antiserum, several groups have reported findings suggesting the application of C-reactive protein measurement as an index of myocardial necrosis.[5-10]

The present study was undertaken to determine whether C-reactive protein appeared so consistently in the blood of patients following acute myocardial infarction as to be useful in the diagnosis and management of this illness. C-reactive protein was also measured in those patients with coronary artery disease who suffered protracted chest pain without apparent development of myocardial necrosis, as demonstrated by other available technics.

Materials and Methods

The 62 patients comprising this study were selected from the Medical Service of The Mount Sinai Hospital and from the private practice of one

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of us (H. L.). They ranged in age from 39 to 83 years. Forty-four were men and 18 were women; 61 were white and one was Negro.

In addition to the clinical examination, urine examinations, complete blood counts, erythrocyte sedimentation rate (Westergren) and electrocardiographic studies were performed at frequent intervals.

Blood was taken for C-reactive protein as soon as possible after admission to the hospital, and repeat blood samples were drawn approximately three times weekly thereafter.

The blood was analyzed for the presence of C-reactive protein according to the method of Anderson and McCarty.[11] One and one-half centimeters of antiserum to C-reactive protein and an equal amount of the patient's serum were drawn into a capillary tube (0.7 to 1.0 mm. outside diameter); the

TABLE 1

Age, Sex and Race Distribution of 50 Patients with Acute Myocardial Infarction

Age (years)	No. of Patients
30–39	1
40–49	12
50–59	13
60–69	15
70–79	7
80–89	2
Sex	
Male	34
Female	16
Race	
White	49
Negro	1

tube was incubated at 37° C. for two hours and then refrigerated at 4° C. overnight. When no visible precipitate was present, the test was considered negative. Each millimeter of precipitate was considered 1 plus; the maximal precipitation was designated 6 plus.

RESULTS

Fifty of the total of 62 patients in this series sustained acute myocardial infarction. The remaining 12 patients manifested coronary insufficiency without apparent myocardial infarction. Analysis of these two groups will be presented separately.

1. *Data on 50 Patients with Acute Myocardial Infarction.*

a. *Clinical and laboratory data:* The age, sex and race distribution of these patients are detailed in table 1. All patients had coronary artery disease and, in addition, eight patients had hypertension. In most instances the patients were admitted to the hospital within 24 hours after the onset of the acute illness. All manifested severe chest pain. Only three patients

gave evidence of shock, occurring during the early stage of the illness; 10 patients displayed congestive heart failure.

Physical examination of the patients revealed the findings typical of acute myocardial infarction: tachycardia, distant heart sounds and low blood pressure. Temperature elevations above 100° F. were present in 44 of the 50 patients. The temperature returned to normal limits within seven days, except for eight patients, who manifested fever for longer periods. Laboratory studies revealed no significant urinary abnormalities. Leukocytosis appeared in 34 patients, and usually remitted within a week. Elevation of the erythrocyte sedimentation rate was noted in 41 patients. Electrocardiographic demonstration of myocardial infarction was indicative of anterior wall infarction in 23 patients, diaphragmatic wall infarction in 12 patients, and combined diaphragmatic and anterior wall infarction in four patients. One patient who had had a right bundle branch block pattern developed T wave inversions in the precordial leads. Nine patients who had abnormalities of the electrocardiogram indicative of previous myocardial infarction had changes in the standard and precordial leads indicative of recent myocardial necrosis. In only one patient was there lack of electrocardiographic confirmation despite classic clinical and laboratory evidence of acute myocardial infarction.

TABLE 2

Time of Initial Blood Sample of C-Reactive Protein after Onset of Pain

Time	No. of Patients
Same day	3
First day	24
Second day	11
Third day	8
Fourth day	2
Fifth day	2

TABLE 3

Maximal Titer of C-Reactive Protein Following Acute Myocardial Infarction

Titer	No. of Patients
0	1
Low (1+)	4
Moderate (2, 3+)	17
High (4+ and above)	28

All patients were treated with bed-rest; 39 patients received anticoagulants as well. The course of hospitalization varied from six days to 75 days, with 41 patients remaining in the hospital for periods of from 15 to 42 days. Five patients died, and necropsies were performed in three of these cases.

b. *C-reactive protein data:* Blood samples for C-reactive protein were obtained as soon as possible after admission to the hospital (table 2). C-reactive protein appeared in the blood of 49 of the 50 patients of this group

TABLE 4

Comparison of Titer and Duration of C-Reactive Protein Following Acute Myocardial Infarction

CRP Titer	1–7 Days	8–14 Days	15–21 Days	22+ Days
Low	4	0	0	0
Moderate	6	8	1	2
High	7	13	2	6

(table 3). Moderate to high amounts of C-reactive protein appeared in most patients. C-reactive protein persisted in the blood for longer periods in those patients in whom its titer was greatest (table 4).

The amount of C-reactive protein in the patients' sera correlated roughly with other laboratory indices of myocardial infarction (figure 1). In those instances in whom moderate or large amounts of C-reactive protein were detected in the blood, fever was more prominent, leukocytosis occurred more regularly, and elevated erythrocyte sedimentation rates were higher and persisted for longer periods. However, no correlation was evident in individual blood samples between its C-reactive protein content and other abnormal blood tests. The amount and duration of C-reactive protein were independent of the particular electrocardiographic pattern of myocardial infarction. The erythrocyte sedimentation rate tended to remain elevated after C-reactive protein was no longer demonstrable in the blood. In nine

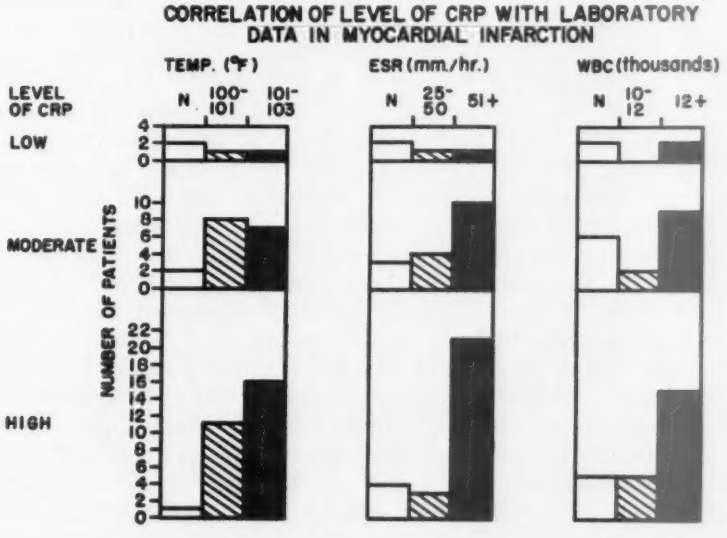

FIG. 1.

patients, however, C-reactive protein was detected in the blood despite the absence of elevation of the erythrocyte sedimentation rate.

In 15 patients, C-reactive protein appeared prior to changes in the electrocardiogram. In 25 instances the abnormal electrocardiogram was present coincident with the appearance of C-reactive protein, whereas in only three patients did the electrocardiogram give evidence of myocardial damage prior to the appearance of C-reactive protein. In the remaining patients it was not possible to compare these tests as to their time of occurrence. The appearance of C-reactive protein in the blood prior to the changes in the electrocardiogram was particularly useful in those patients who had abnormalities of the electrocardiogram indicating previous myocardial infarction. The changes in the electrocardiogram indicative of acute infarction were often masked for several days from the onset of the illness, and the appearance of C-reactive protein in the blood heralded the forthcoming electrocardiographic changes.

TABLE 5

Patterns of C-Reactive Protein in Acute Myocardial Infarction

Type	No. of Patients
Persistently 0	1
0 → + → 0	7
+ → 0	29
Persistently +	4
Nonclassifiable	9

Although the sera of 49 of the 50 patients in the series contained C-reactive protein, the particular pattern of appearance and disappearance of this protein varied (table 5). In 29 patients, C-reactive protein appeared in the initial blood specimens and persisted for variable periods, after which it could not be detected. In seven patients, initial blood specimens did not contain C-reactive protein. The blood samples of two of these seven patients were obtained during the prodromata of the coronary occlusion, at a time when clinical and laboratory evidences of myocardial infarction were absent. Blood samples taken subsequent to the coronary thrombosis contained C-reactive protein, which appeared in a manner similar to that of the preceding group. In the remaining five patients, C-reactive protein did not appear for from 24 to 48 hours following the acute myocardial infarction, and initial blood specimens did not contain the abnormal protein. C-reactive protein remained in the blood of four patients during the entire period of hospitalization. Of these, two patients died eight and 11 days, respectively, after acute myocardial infarction. In the remaining nine patients, C-protein was intermittently present. In most instances of reappearance of C-reactive protein an explanation for its return was apparent, as, for example, pulmonary infection or infarction, congestive heart failure, or extension of myocardial infarction. In only one patient in whom myocardial infarction

was demonstrated was C-reactive protein absent from serial blood specimens.

c. *Mortality data:* Table 6 summarizes the data in five patients who died following acute myocardial infarction. At the time of death, three patients had C-reactive protein in the preterminal blood specimen. These specimens were obtained three, eight and 11 days, respectively, following the infarction. In two patients C-reactive protein had disappeared prior to death. Necropsy findings in three of these patients confirmed the presence of acute myocardial infarction secondary to coronary thrombosis.

2. Data of 12 Patients with Chest Pain of Coronary Origin without Apparent Myocardial Infarction.

The sera of 12 patients admitted to the hospital because of protracted chest pain suggesting acute myocardial infarction were studied serially. None of these patients was found to have sustained a myocardial infarction, although all had established coronary artery disease. Ten were male and two were female; their ages ranged from 43 to 72 years; all were white.

TABLE 6

Data of Five Patients Who Died Following Acute Myocardial Infarction

Patient	CRP Pattern	Level of CRP	Duration of CRP (days)	Necropsy
M. L.	Persistently +	High	11	Yes
L. S.	+ → 0	High	8	Yes
M. R.	+ → 0	Moderate	27	No
N. R.	Persistently +	High	8	No
I. F.	0 → +	High	3	Yes

Chest pain of varying intensity lasted from one to 10 hours. Four patients had associated hypertension and, in addition, one instance each of polycythemia, rheumatic heart disease, congenital heart disease, gall-bladder disease and diabetes was found in five other patients. None demonstrated shock, and in only one patient was there mild congestive heart failure. Temperatures were normal except for elevation between 100 and 101° F. in two patients. Leukocytosis was present in two patients, one of whom had polycythemia. The erythrocyte sedimentation rate was minimally elevated in five patients.

In nine patients, blood samples were obtained and analyzed for C-reactive protein within 48 hours after onset of chest pain, while in three patients, blood was obtained four to six days following the acute chest pain. The electrocardiograms of five of these patients showed a pattern of coronary insufficiency with ST segment depressions and T wave inversions; in one instance this was associated with intermittent Wolff-Parkinson-White syndrome. The electrocardiograms of eight patients demonstrated previous myocardial infarction without any progressive changes.

C-reactive protein was absent from all blood specimens in this group.

Case Reports

Case 1. A 61 year old white man (figure 2) had had symptoms of coronary artery disease for many years. Onset of severe precordial chest pain radiating to both shoulders and arms, associated with profound sweating, was sudden; five hours later, still in pain, he was admitted to The Mount Sinai Hospital.

At the time of admission he was acutely ill. The heart was not enlarged; the sounds were of fair intensity. The heart rate was 96 per minute. The blood pressure was 140/60 mm. mercury. There were no signs of congestive heart failure.

Laboratory studies revealed a normal urine and hemoglobin. The white blood count was 11,400 cells per cubic millimeter, and the sedimentation rate was 62 mm./hr. (Westergren). The electrocardiogram indicated an anterior wall myocardial infarction, and progressive changes were manifest in subsequent electrocardiograms.

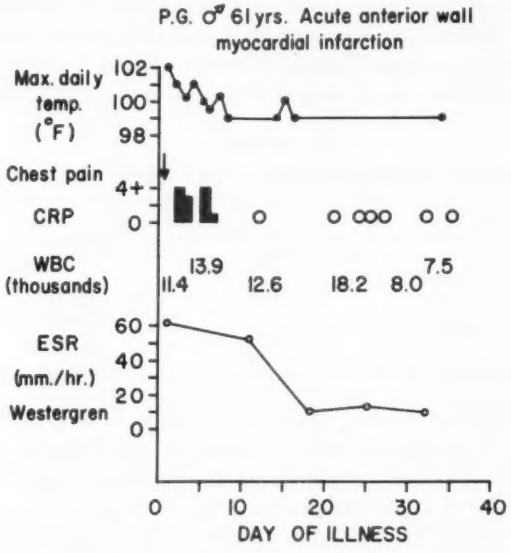

Fig. 2.

The course is detailed in figure 2. The patient was treated with bed-rest and was given anticoagulants. The admission temperature of 102° F. returned to normal levels within the first week. The white blood count remained elevated for 22 days, whereas the erythrocyte sedimentation rate returned to normal levels within 17 days. His hospital course was uneventful and uncomplicated.

Blood samples taken immediately following admission contained large amounts of C-reactive protein. Blood samples taken during the first week also contained C-reactive protein, but thereafter no C-reactive protein was demonstrable in the patient's blood.

Comment: This case illustrates the typical findings in which C-reactive protein appears promptly following acute myocardial infarction. It remained in the patient's serum for seven days, despite the persistence of

leukocytosis and an elevated erythrocyte sedimentation rate for longer periods.

Case 2. A 54 year old white man (figure 3) had experienced acute myocardial infarctions five and two years previously. Four days prior to his admission to The Mount Sinai Hospital he had developed severe chest pain, lasting five minutes at a time and recurring four to five times daily. The pain occurred with any exertion and responded quickly to rest and the sublingual administration of nitroglycerin. Because of the persistence of the pain he was referred to the hospital.

Physical examination was unremarkable. The heart was normal in size and the heart sounds were of good quality. Regular sinus rhythm was present, with a rate of 80 per minute. The blood pressure was 110/70 mm. of mercury. Urine examination was normal. The hemoglobin was 17.6 gm.%; the red blood count, 6.3

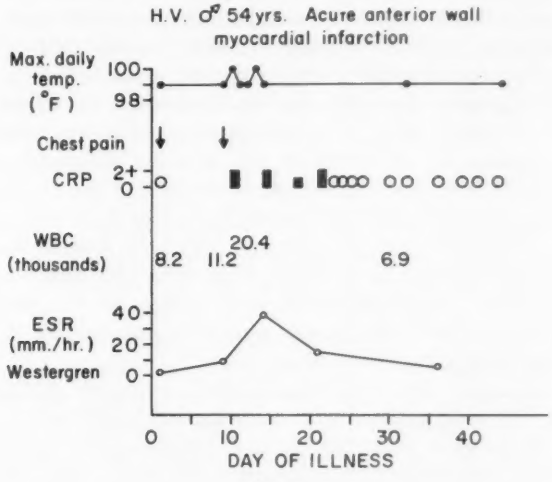

FIG. 3.

million cells per cubic millimeter; hematocrit, 59%. The white blood count was 8,200 cells per cubic millimeter, with a normal differential count. The erythrocyte sedimentation rate was 2 mm. per hour (Westergren). The initial electrocardiogram was unchanged from previous records, which showed past diaphragmatic wall myocardial infarction.

During the first eight days of his hospital stay the patient was asymptomatic and afebrile. On the ninth hospital day, severe crushing substernal chest pain appeared which radiated to the left shoulder and arm. The pain was treated with parenteral analgesics and remitted after one hour. Following this episode of pain the temperature rose to 100° F. Leukocytosis appeared, and the erythrocyte sedimentation rate became rapid (figure 3). The electrocardiogram gave evidence of an acute anterolateral wall myocardial infarction. The patient's course following this episode was uneventful. He was treated with bed-rest and anticoagulants. Fever remitted, the leukocytosis disappeared and the erythrocyte sedimentation rate returned to normal.

A blood specimen taken on the first hospital day contained no C-reactive protein.

On the day following the acute myocardial infarction, however, moderate amounts of C-reactive protein appeared and persisted in the patient's blood for 11 days.

Comment: In this instance the presence of C-reactive protein closely mirrored other laboratory manifestations of myocardial infarction. A blood specimen obtained during the prodromata of the coronary thrombosis did not contain C-reactive protein. This protein, however, appeared within 24 hours following the myocardial infarction, indicating its usefulness as an additional laboratory measure of necrosis.

Discussion

When a patient with established coronary artery disease develops protracted chest pain, it is important to establish the presence or absence of myocardial necrosis in order to institute the proper therapy. Various clinical and laboratory parameters are available for this purpose. In most instances the diagnosis is made when the patient presents the classic clinical and electrocardiographic findings. In instances where evolution of electrocardiographic changes is slow, or in the presence of a previously abnormal electrocardiogram, other measures to aid in exact diagnosis are sought. The appearance of fever, leukocytosis and elevation of the erythrocyte sedimentation rate, although each is nonspecific, is useful to this end. Other tests, such as serum complement, glutamic oxalacetic transaminase activity, mucoprotein content of the blood, blood fibrinogen level and urinary coproporphyrin excretion, have been shown to be helpful in this regard.[9, 10, 12–14] Serum C-reactive protein content has also been proposed as an additional laboratory index of myocardial necrosis.

The present study has demonstrated that C-reactive protein appeared in the blood of 49 of 50 patients with acute myocardial infarction, and failed to appear in 12 patients with chest pain who did not develop other clinical or laboratory manifestations of myocardial necrosis. The appearance of C-reactive protein in the blood of 15 patients prior to the appearance of the electrocardiographic changes suggests that this measurement may have clinical usefulness in the very early detection of myocardial infarction. This is particularly true in those instances in which, as a result of previous myocardial infarction, a grossly abnormal electrocardiogram was present before the recent episode of chest pain. The early appearance of serum C-reactive protein in these cases aids in the diagnosis of myocardial infarction. However, a single blood specimen that fails to contain C-reactive protein cannot be relied upon to reject the diagnosis of myocardial necrosis, for, as was demonstrated in a few instances, C-reactive protein may not appear in the blood until 48 hours after acute myocardial infarction.

An additional advantage for the clinical application of the C-reactive protein measurement is the rapid changes that occur in the presence of C-reactive protein after acute myocardial infarction. Following a single myocardial insult, the C-reactive protein appears and disappears, usually

in from one to two weeks, whereas the erythrocyte sedimentation rate usually remains elevated for longer periods and the electrocardiogram may continue to undergo progressive changes for weeks or months. In this way, the C-reactive protein appeared to be a more sensitive indicator of the acute process than did the sedimentation rate. Further study is indicated in states of coronary insufficiency to determine how much necrosis is necessary to result in the appearance of C-reactive protein.

One limitation of C-reactive protein as a diagnostic test is its lack of specificity. It appears in response to a variety of stimuli, such as trauma, infection, necrosis, neoplasia, and granuloma formation.[1, 4, 15] Indeed, it has been demonstrated to appear in the blood of patients with congestive heart failure.[16] Thus its appearance cannot be utilized to differentiate myocardial infarction from other acute medical catastrophes, such as pulmonary infarction, myocarditis, pericarditis or acute cholecystitis. Despite its lack of specificity, it has proved more useful than other nonspecific indicators of the inflammatory reaction in diseases, such as acute rheumatic fever [17] and the postcommissurotomy syndrome.[18]

Summary

Fifty patients with acute myocardial infarction have been studied with serial blood determinations for C-reactive protein. This abnormal protein was found in 49 instances. The amount of C-reactive protein correlated roughly with other laboratory indices of infarction, such as fever, leukocytosis and elevated erythrocyte sedimentation rate. In approximately 60% of these patients, C-reactive protein was initially present but disappeared after one to two weeks following the myocardial infarction. In seven patients C-protein was absent from the initial blood specimens but appeared within one to two days and then disappeared in a manner similar to that of the preceding group. In four patients C-reactive protein persisted in the blood, and in nine cases there was no discernible pattern.

Twelve patients with coronary artery disease with protracted chest pain indicative of coronary insufficiency but without apparent myocardial infarction have been studied with serial blood determinations for C-reactive protein. In no instance was C-reactive protein present.

The C-reactive protein test is suggested as an additional useful and sensitive laboratory aid in the diagnosis of myocardial infarction.

Summario in Interlingua

Cinquanta patientes con acute infarcimento myocardial esseva studiate per un technica de determinationes serial de proteina C-reactive. Iste proteina anormal esseva trovate in 49 casos. Le nivellos de proteina C-reactive esseva grossiermente correlationate con altere indicios de infarcimento, como per exemplo febre, leucocytosis, e acceleration del sedimentation erythrocytic. In circa 60% de iste patientes, proteina C-reactive esseva presente initialmente sed dispareva post un a duo septimanas a partir del infarcimento myocardial. In septe patientes, proteina C-reactive

esseva absente ab le prime specimens de sanguine, sed illo appareva intra un a duo dies e dispareva subsequentemente in un maniera simile a su disparition in le altere casos. In quatro patientes, proteina C-reactive persisteva in le sanguine, e in nove casos illo occurreva intermittentemente sin obvie schema regular.

Dece-duo patientes con morbo de arteria coronari, con prolongate dolores thoracic indicante insufficientia coronari sed sin apparente infarcimento myocardial, esseva studiate per le mesme technica de determinationes serial de proteina C-reactive. Nulle proteina C-reactive esseva presente in ulle caso de iste gruppo.

Le test pro proteina C-reactive es proponite como un utile e sensibile addition al adjutas laboratorial in le diagnose de infarcimento myocardial.

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THE VALUE OF THE C-REACTIVE PROTEIN DETERMINATION IN CORONARY ARTERY DISEASE *

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THE C-reactive protein test is a highly sensitive test for the presence of acute inflammation. The capsule of the pneumococcus bacterium contains a specific polysaccharide called C polysaccharide, which behaves as a specific antigen. If one studies the sera of patients with pneumonitis of pneumococcal origin, an antibody for this C polysaccharide can be demonstrated. The antibody is a protein and has been named C-reactive protein.

In 1930 Tillet and Francis [1] demonstrated for the first time the presence of the above substance in a patient with pneumococcal pneumonitis. Later they observed that this substance was found only in sera of patients with diseases associated with acute inflammation. The substance was no longer detected when the acute process had subsided. Based upon the presence of C-reactive protein in the sera of patients with certain inflammatory diseases, characteristic precipitin reactions graded negative to 4 plus developed upon the addition of C-reactive protein rabbit anti-serum to sera of such patients. C-reactive protein was never found in normal serum.

MacLeod and Avery,[2] Wood [3] and McCarty [4] isolated and identified the protein reported by Tillet and Francis [1] by electrophoretic separation. When this protein was injected into rabbits a specific antiserum was obtained. It was this antiserum that produced a precipitate when added to the sera of patients with active inflammatory disease.

C-reactive protein is a nonspecific test, yet an extremely sensitive index of inflammation. Until now the test most widely employed to determine the presence and extent of an acute inflammatory process has been the erythrocyte sedimentation rate. Unfortunately, a multiplicity of factors unrelated to inflammation can influence this test and give misleading results. Anemia, increased fibrinogen, and increases in the alpha and gamma globulins hasten the rate of fall. Albumin, on the other hand, retards the rate of fall. In pregnancy the sedimentation rate is increased coincident with the increase in fibrinogen. In some infectious diseases the fibrinogen content is markedly increased and remains elevated after the acute process has subsided. This is due to the extremely slow fall in the fibrinogen level to normal. In congestive heart failure the fibrinogen level is decreased as a result of passive congestion of the liver. In such patients the sedimentation

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rate is frequently normal, irrespective of whether an acute inflammatory process is present. In contrast, the C-reactive protein determination depends upon only one factor, namely, the presence of C-reactive protein in the serum of a patient.

C-reactive protein appears within 14 to 24 hours after acute inflammation has occurred. The introduction of a commercial antiserum (C.R.P.A.) * has made the detection of C-reactive protein a very practical procedure for any hospital or office laboratory. Actually, it is a simple precipitation reaction that can be done in a physician's office. The method employed in our determination of the C-reactive protein is given below.†

1. Draw up the C.R.P.A. to one third of the 90 mm. capillary tube length. Keep finger over top of tube.
2. Wipe the capillary tube clean.
3. Draw up enough of the patient's serum into the capillary tube that the tube is two thirds full, i.e., one third C.R.P.A. and one third serum.
4. Place finger over the top of the capillary tube and slowly invert the tube several times to insure proper mixture of C.R.P.A. and serum.
5. Place the capillary tube into the modeling clay rack, making sure that the bottom of the fluid column in the capillary tube is 5 to 10 mm. above the clay.
6. Place rack in incubator set at about 37° C. for two hours to obtain maximal precipitation. At the end of this time a reading can be made to determine the preliminary quantitative aspect of the reaction, as well as definite qualitative readings. (At the end of 30 minutes a characteristic precipitate will begin to form if C-reactive protein is present in the patient's serum.) Readings are best made against a dark background, using oblique illumination. If an incubator is not available, acceptable readings may be made with room temperature over a period of several hours.
7. Remove rack from incubator and place in refrigerator overnight. At the end of this time a final semiquantitative reading may be made. It must be borne in mind that packing may not have occurred. In such cases, where the precipitate is dispersed throughout the fluid column, a quantitative reading may be obtained from the summation of the total dispersed precipitate. The readings may be evaluated as follows:

No visible reaction = 0
A definite but slight reaction = 1 plus (approximately 1 mm. precipitate)
Moderately strong reaction = 2 plus
Strong reaction = 3 plus
Very strong reaction = 4 plus

Myocardial infarction is an acute inflammatory process. In the past the attempt has been made to correlate the extent of the infarction with the rise in sedimentation rate, leukocytosis and febrile response. Necrotic myocardial tissue behaves like an aseptic inflammation and liberates several foreign protein products. Various immunobiologic phenomena occur as a result of this protein liberation. Beta globulin has been shown to be increased in acute myocardial infarction by electrophoretic studies. C-reactive protein is believed to be a fraction of the beta globulin. Some unknown

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qualitative changes occur in the beta globulin fraction after acute myocardial infarction. The changed beta globulin acts like C-reactive protein. This abnormal serum globulin is formed by the body in response to such varied stimuli as tissue necrosis, infection and neoplasm. C-reactive protein has been a very useful agent as an adjunct in the diagnosis and evaluation of the therapeutic response in rheumatic fever.[5, 6, 7] Investigators have found the C-reactive protein consistently negative in uncomplicated congestive heart failure and coronary insufficiency without infarction.[8]

In our study the C-reactive protein test was performed with the sera of 100 patients who had sustained an acute myocardial infarction with unequivocal electrocardiographic, autopsy or combined confirmation of the diagnosis. C-reactive protein was detected in every myocardial infarction patient with significant Q waves in the electrocardiogram. There was a delayed positive test in some of the patients, indicating that a degree of necrosis in the myocardium must be present before the C-reactive protein is detected in the serum. It was absent in 50 cases of coronary insufficiency studied without recent or old myocardial infarction. C-reactive protein was absent initially during the so-called "premonitory phase" of acute coronary occlusion, before the appearance of the clinical evidence of necrosis and the electrocardiographic changes diagnostic of this condition. It was absent in 25 patients with the "coronary failure" syndrome. Serial C-reactive protein determinations were done in the myocardial infarction patients, and also in the coronary insufficiency and the "coronary failure" patients. Twenty-five patients with a history and electrocardiographic evidence of previous myocardial infarction two months or older in duration were studied. The C-reactive protein was consistently negative in these patients. Negative C-reactive protein results on normal individuals and positive results in patients with pneumococcal pneumonitis, acute rheumatic fever, pulmonary infarction, thrombophlebitis and other diverse inflammatory conditions are not recorded in this paper, although they were studied concurrently with the myocardial infarction patients. These have been reported previously by other investigators in great detail. From the above group of patients, 40 were selected and divided into four categories to demonstrate our various experiences with C-reactive protein in coronary artery disease. Serial C-reactive protein determinations, sedimentation rates (Westergren method), electrocardiograms and frequent clinical observations were done on these selected patients.

The first category demonstrates the expected C-reactive protein reaction in a typical uncomplicated acute myocardial infarction patient.

Case Reports

Case 1. A 52 year old white male factory worker was admitted to the hospital with a history of having sustained a myocardial infarction three years previously. At the time of admission he had had severe retrosternal pain for one hour, with marked diaphoresis. The initial electrocardiogram showed partial AV block (first

degree), and evidence of an old anterior myocardial infarction. There was no electrocardiographic evidence of a recent myocardial infarction. The C-reactive protein was 3 plus 24 hours after admission. Serial electrocardiograms 72 hours later showed definite changes from the admission electrocardiogram, and were diagnostic of a recent acute posterior myocardial infarction. The C-reactive protein at this time was still 3 plus. Serial electrocardiograms showed progressive healing, and the C-reactive protein test became 1 plus on the ninth hospital day and was negative the fourteenth day. Sedimentation rates were 13 mm. at 24 hours, 17 mm. on the ninth hospital day, and 18 mm. on the fourteenth day.

The above response is representative of 20 selected patients followed serially in the same manner, and showing the usual, expected response to the C-reactive protein test in a known acute uncomplicated myocardial infarction patient. During the 24 hours following infarction, the C-reactive protein became abnormal more rapidly than did the sedimentation rate in the patients studied. During the recuperative period the C-reactive protein test tended to become negative more rapidly than did the sedimentation rate. The persistence of a positive C-reactive protein test was usually indicative of a progressive infarction, phlebothrombosis or some other embolic complication, as will be demonstrated in subsequent complicated patients.

The second category demonstrates how the C-reactive protein test may be an adjunct to the degree of leukocytosis, the sedimentation rate, the electrocardiogram, the clinical course and the febrile response in attempting to estimate the prognosis of acute myocardial infarction.

Case 2. A 54 year old white male executive was admitted with a history suggestive but not diagnostic of acute coronary thrombosis. Admission electrocardiogram on October 21, 1954, revealed only acute anterior myocardial anoxemia. The C-reactive protein was negative on admission. Serial electrocardiograms on October 23 revealed changes diagnostic of acute anterior myocardial infarction. The C-reactive protein was 4 plus at this time and remained strongly positive for the next three days. It was 1 plus when the patient was discharged to his home for further convalescence on November 10. At the time of discharge the electrocardiogram continued to show minimal ST segment elevation in the unipolar precordial leads. The patient remained at home approximately four weeks. He was confined to bed the first week and gradually ambulated; however, on December 6 he was re-admitted with severe precordial pain, shock and marked diaphoresis. An electrocardiogram on December 6 revealed, in addition to the old anterior myocardial infarction, an acute posterior myocardial infarction. The C-reactive protein was 4 plus. It was 4 plus on December 12, and remained 4 plus until death, 19 days after admission. The last test was done on December 18, 24 hours prior to death.

The C-reactive protein response was typical of that in 10 other selected patients, in whom it failed to go through the usual normal evolution and remained at the 4 plus level beyond the expected fall period. It has been interesting to note that, where the C-reactive protein test remained 4 plus throughout the hospital stay, nine of the patients died. One, although surviving the hospital stay, succumbed two weeks after discharge from the hospital. All of these patients were treated in the conventional manner, with anticoagulants employed in the effective prothrombin range. No un-

usual arrhythmia was noted in these 10 cases. Clinically all had the appearance of massive myocardial infarction with severe, persistent shock. Levophed therapy was employed in six of the 10 patients. Sedimentation rates in these patients did not parallel the C-reactive protein results and the serial electrocardiographic findings.

The third category demonstrates the value of C-reactive protein in helping to differentiate acute myocardial infarction from "coronary failure" syndrome.

Case 3. A 76 year old retired white male was admitted with acute precordial distress of one hour's duration and with mild diaphoresis. The initial electrocardiogram showed inverted and cove-shaped T waves in Leads 2, 3 and aVF, and complete right bundle branch block. No significant Q waves or ST segment elevation were present. Serial electrocardiograms revealed no significant change other than minor T wave changes. The C-reactive protein was negative on admission and remained negative on four tests throughout the 14 days in the hospital. Sedimentation rate was 33 mm. on admission and varied between 38 mm. and 22 mm. during the hospital stay. The patient had an uneventful convalescence and was discharged on the fourteenth day. The clinical impression, substantiated by our C-reactive protein tests, was that this patient had a "coronary failure" syndrome and had not sustained an acute myocardial infarction. One year has elapsed since this patient's discharge, and he has not sustained any evidence of coronary occlusion clinically or from the electrocardiographic standpoint.

The above response is typical of that of 10 selected patients of this type. The C-reactive protein has been negative in all patients with coronary insufficiency who had no clinical or laboratory criteria for myocardial necrosis. It has been helpful in several patients in whom a diagnosis could not be definitely established clinically and the electrocardiogram unfortunately revealed complete left bundle branch block, which obscured the electrocardiographic diagnosis of myocardial infarction with certainty. The C-reactive protein was consistently negative in the patients felt subsequently not to have sustained a myocardial infarction, but positive in cases where myocardial infarction was proved by autopsy.

The fourth category represents a group of patients with an equivocal clinical history of recent infarction who had previously sustained an infarction, with present electrocardiographic findings of indeterminate age. Where the clinical course and serial electrocardiograms subsequently made possible a definite diagnosis of old infarction and no recent infarction, the C-reactive protein serially was consistently negative.

Case 4. A 70 year old retired banker was admitted with severe retrosternal pain of 30 minutes' duration associated with diaphoresis and minimal Q wave in Leads 2, 3 and aVF, with inverted and cove-shaped T waves associated with complete right bundle branch block. It was difficult to state from the electrocardiogram whether this was an acute or old process. Serial electrocardiograms on the third, the seventh and the twentieth hospital days did not reveal any significant changes. C-reactive protein tests done at the same time were negative. The sedimentation rate remained at 38 mm. per hour during the hospital stay. The patient had an uneventful convalescence. It was the feeling that clinically, electrocardiographically and

by the C-reactive protein test the electrocardiographic findings were of remote rather than recent origin.

This response was typical of that of 10 other selected patients in whom the C-reactive protein tests aided in differentiating between recent and remote electrocardiographic findings where the clinical history and the electrocardiographic findings were equivocal as to the age of infarction.

Conclusion

The C-reactive protein test is a highly sensitive test for acute inflammation, and is superior to the sedimentation rate in following the course of acute inflammation. C-reactive protein tests were done on 200 patients with coronary artery disease. Forty patients were studied with serial C-reactive protein determinations, electrocardiograms, sedimentation rates and frequent clinical observation.

The following conclusions were drawn as to C-reactive protein:

1. It is not a specific test for myocardial infarction; however, it seems to be an excellent adjunct in both the diagnosis and the prognosis of myocardial infarction.
2. It is more reliable than the sedimentation rate in following the natural evolution of myocardial infarction.
3. It is highly positive in patients with acute myocardial infarction, and qualitative changes in C-reactive protein follow clinical and electrocardiographic improvement.
4. It is negative in healed infarctions, coronary insufficiency and "coronary failure" syndrome.
5. It is negative in the premonitory phase of myocardial infarction.
6. The persistence of a positive C-reactive protein test is usually indicative of progressive infarction, phlebothrombosis or some other embolic phenomenon.

Summario in Interlingua

Le test de proteina C-reactive es non-specific, sed le presentia de proteina C-reactive es un sensibilissime indicator de inflammation. Usque nunc le test usate le plus extensemente pro demonstrar le presentia e determinar le grado de un acute processo inflammatori ha essite le mesuration del rapiditate del sedimentation erythrocytic. Infelicemente, un multiplicitate de factores sin relation a processos inflammatori pote influentiar le rapiditate del sedimentation erythrocytic e effectuar resultatos deceptori. Le infarcimento del myocardio es un inflammation aseptic que delivra alien productos proteinic. Le alterate globulina beta age como proteina C-reactive.

In nostre studio le test pro proteina C-reactive esseva executate con le seros de 100 patientes qui habeva suffrite un acute infarcimento myocardial con confirmation inequivoc del diagnose per electrocardiographia o necropsia o ambes. Proteina C-reactive esseva detegite in omne patiente de infarcimento myocardial con significative alterationes electrocardiographic del unda Q. In un certe procentage del patientes, le reaction positive esseva retardate. Isto indica que un grado specific

de necrosis myocardial debe esser presente ante que proteina C-reactive pote esser detegite in le sero. Proteina C-reactive esseva absente in 50 casos de insufficientia coronari sin recente o ancian infarcimento myocardial. Proteina C-reactive esseva absente initialmente durante le si-appellate "phase premonitori" de acute occlusion coronari, precedente le apparition de manifestationes clinic de necrosis e le alterationes electrocardiographic que es diagnostic in iste condition. Proteina C-reactive esseva absente in 25 casos de patientes con le syndrome de "disfallimento coronari." Esseva studiate 25 patientes con un historia o un electrocardiogramma indicante le previe occurrentia de infarcimento myocardial de un duration de duo menses o plus. Proteina C-reactive esseva uniformemente absente in iste casos de occurrentias passate de infarcimento. Es presentate le historias de casos individual que illustra le supra-listate constatationes.

Le sequente conclusiones esseva derivate: (1) Le determination de proteina C-reactive non es un test specific pro infarcimento myocardial. Il pare, nonobstante, que illo representa un excellente adjuta in tanto le diagnose como etiam le prognose de infarcimento myocardial. (2) Proteina C-reactive reflecte le evolution natural de infarcimento myocardial plus fidelmente que le rapiditate del sedimentation erythrocytic. (3) Le test pro proteina C-reactive es positivissime in patientes con acute infarcimento myocardial. Alterationes qualitative de proteina C-reactive se manifesta post meliorationes clinic e electrocardiographic. (4) Le test pro proteina C-reactive es negative in casos de infarcimento curate, de insufficientia coronari, e del syndrome de "disfallimento coronari." (5) Le test pro proteina C-reactive es negative durante le phase premonitori de infarcimento myocardial. (6) Le persistente presentia de proteina C-reactive es usualmente un indication de infarcimento progressive, phlebothrombosis, o alicun altere phenomeno embolic.

Infelicemente, le test de proteina C-reactive non differentia inter acute infarcimento myocardial e acute pericarditis o infarcimento pulmonar.

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DIAGNOSIS, TREATMENT AND PREVENTION OF CHRONIC HYPERCORTISONISM IN PATIENTS WITH RHEUMATOID ARTHRITIS *

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In the relatively brief period of six years of intensive clinical and biochemical investigations, the great potency of cortisone, corticotropin and related adrenocortical hormonal preparations has been demonstrated.[1] However, knowledge as to how the various effects of these hormones are mediated and how they may be used therapeutically to best advantage and with greatest safety is still incomplete.

The therapeutic use of cortisone or its analogues or corticotropin must still be based on careful consideration of both the anticipated benefits and the potential disadvantages of the hormone for each disease and each patient. These considerations become especially important when long-term hormonal treatment is undertaken. The calculated, acceptable (or unacceptable) risk embodied in the decision to use (or not to use) hormonal treatment has been epitomized in the word "hypercortisonism." [2]

In this presentation we propose (1) to emphasize the significant features of hypercortisonism in patients with rheumatoid arthritis, and (2) to describe certain principles and practices helpful in the management or prevention of chronic hypercortisonism in such patients.

Definition of Hypercortisonism

The term "hypercortisonism" has been given both general and restricted meanings. In a general sense, hypercortisonism is regarded by some as synonymous with hypercorticalism, hyperadrenocorticism and even hyperadrenalism. However, each of these terms has or should have fairly specific connotations which serve to differentiate them broadly from each other.

Restrictive Meanings. In its strictest sense, *hypercortisonism* means an excess of only one substance, cortisone, and could occur, as far as we know now, only during treatment with excessive doses of cortisone (exogenous hypercortisonism). The many similarities between patients with Cushing's

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disease and patients who have received cortisone or related preparations exogenously suggest that Cushing's disease may be a manifestation of endogenous hypercortisonism.[3] But this connotation may prove to be too restrictive, since presently available evidence indicates that the hyperfunctioning adrenal cortex rarely, if ever, produces an excess of just one adrenocortical hormone. The effects of an excess of cortisone are so complex and involve such incompletely defined relationships between the adrenal cortex and other glands that the literal implications of the term "hypercortisonism" are too restrictive for satisfactory current clinical or therapeutic usage.

Hypercorticalism properly represents a more inclusive biochemical state resulting from an excess of more than one or possibly all of the adrenocortical steroids. This may result endogenously from an excess of corticotropin or exogenously from administration of corticotropin in doses sufficient to produce adrenocortical stimulation.

Hyperadrenocorticism is a term used synonymously with hypercorticalism as described above.

Hyperadrenalism is an even less specific term which, though used synonymously at times with hypercorticalism or even hypercortisonism, literally implies hyperfunction of both cortical and medullary portions of the adrenal gland. Studies on a few patients who seemingly exhibited this phenomenon have been reported,[4-6] but this is apparently an extremely rare entity which differs in certain respects from the effects produced by the adrenocortical hormones alone.

Practical Application of Terminology. The more restrictive connotations are of course more precise, but before the current terminology can be defined accurately or improved, more information is needed concerning the quantitative relationship of the various adrenocortical hormones to each other under various circumstances. Actually, hypercortisonism from administration of cortisone or its analogues is a composite of exogenous *hyper*cortisonism plus endogenous *hypo*cortisonism (or hypocorticalism or hypoadrenocorticism), while hypercortisonism from administration of corticotropin is a composite of endogenous *hyper*corticalism plus endogenous anterior *hypo*pituitarism. In each instance modifying effects on other glands and bodily tissues must be considered also.

As the term "hypercortisonism" is currently used clinically, it represents not merely an excess of cortisone alone, but rather encompasses also both the direct and the indirect effects of administration of other related effective adrenocortical hormones as well as cortisone, or the effects of endogenous stimulation of the adrenal cortex resulting from administration of corticotropin.

Hypercortisonism may be mild, moderate or severe, and may occur either acutely or chronically, with somewhat different developments in each instance.

Acute hypercortisonism almost always develops during use of large doses of cortisone or related preparations, either in the short-term treatment of acute or serious but self-limited diseases, or in the initial period of long-term treatment of chronic diseases.

Signs of acute hypercortisonism generally develop quickly, usually within the first few days or weeks, depending on the doses of the hormone given, duration of administration, and the age, sex and tolerance of the patient.

The most common signs and symptoms of acute hypercortisonism include one or more of the following: excessive appetite and gain in weight, euphoria, insomnia, increased nervous tension and irritability, facial rounding, increase of fat pads, particularly in supraclavicular and posterior cervical regions, retention of fluid, edema, irregular menses, acne and hypertrichosis. Other manifestations, equally familiar, might be included also.[2, 3, 7-17]

The problems of the management of acute hypercortisonism may be simplified by the self-limiting nature of the disease for which the cortisone or other hormonal preparation is given, as this thus limits the duration of hormonal treatment. But acute hypercortisonism should be tolerated only if the seriousness of the disease being treated makes further treatment with the hormone imperative, or if the course of treatment is to be of relatively short duration.

Chronic hypercortisonism, by contrast, results from prolonged overdosage with cortisone or related preparations, even though the overdosage is mild and perhaps unsuspected, and usually develops insidiously over weeks or months during use of excessive maintenance doses in long-term treatment of chronic diseases. The degree and rate of development of chronic hypercortisonism vary with the amount of hormone, duration of administration, age and sex of the patient, and possibly with the severity of the systemic reaction of the disease. It may develop in as short a time as two months from beginning of treatment, especially in susceptible patients, or it may not become apparent until after a year or more of treatment.

The currently inadequate understanding of many aspects of chronic hypercortisonism and difficulty in recognizing the condition early may contribute to its progression from mild to more severe stages. As experience with use of adrenocortical hormones as therapeutic agents is accumulated, it has become more and more evident that the mesenchymal tissues of patients with different diseases may respond differently to hormonal therapy. This is evident not only in the tolerance for various doses used in different diseases but also in the tolerance of various patients to withdrawal after prolonged hormonal treatment in different diseases. Patients given adrenocortical hormonal treatment for leukemia,[18] osteoarthritis [18] and asthma,[19] for example, tolerate cessation of hormonal therapy much more satisfactorily than similarly treated patients with rheumatoid arthritis or lupus erythematosus.

Features of Chronic Hypercortisonism in Patients With Rheumatoid Arthritis

The chronic hypercortisonism in patients with rheumatoid arthritis occurs only after the usual signs and symptoms of acute hypercortisonism have been present for weeks or months. The time of the development of chronic hypercortisonism depends on the dosage, duration of administration and susceptibility of the patient. Women past menopause are the most susceptible of adults; men are the least susceptible to chronic hypercortisonism. Men usually require more adrenal steroid for a therapeutic effect than women with similar disease, and men have far fewer of the undesirable effects of overdosage than women. Usually chronic hypercortisonism does not become clinically evident in less than two months of treatment with doses of 75 to 100 mg. of cortisone daily (or comparable doses of other antirheumatically effective steroids). Chronic hypercortisonism, however, may be delayed for months with smaller but excessive doses of these substances.

The characteristic feature of chronic hypercortisonism is the appearance of cyclic swings of mood and symptoms. Increased fatigability, muscular and joint aching, and emotional instability alternate with periods of stimulation associated with a "restless drive" and relatively little aching. The relative predominance of either part of the cycle varies from patient to patient. Pertinent details are at times elicited with difficulty or perhaps not at all initially from the patient. Repeated interviews with the patient and his family and repeated detailed observations of both the periods of relative well-being and depression may be needed to recognize the extent of the manifestations of chronic hormonal overdosage in a rheumatoid patient.

During periods of relative well-being, the patient is alert, coöperative and active. When depressed, the patient may be unable to concentrate normally; coöperation as well as activity is restricted. Spontaneous crying spells may occur. In general, the patient feels better with rest and worse with fatigue. Activities such as shopping and cooking may be interrupted by quickly developing severe physical and mental fatigue. Patients are often reluctant or unable, at least in early interviews, to report these events.

Symptoms are accentuated when the time is greatest from the last dose of the hormone. The next dose or increase in dosage may partially improve the symptoms of chronic hypercortisonism in the rheumatoid patient, but only temporarily. However, successive increases of dosage accentuate the cyclic swings of symptoms, and may complicate the course of symptoms resulting from chronic hypercortisonism.

Differentiation of Musculoskeletal Symptoms of Hypercortisonism from Those of a Flare of Rheumatoid Arthritis. Mesenchymal reactions due to chronic hypercortisonism must be differentiated from flares of rheumatoid

arthritis due to inadequate dosage of steroids, and also from flares due to misuse of previously damaged rheumatoid joints. In chronic hypercortisonism synovitis is minimal or not increased. A rheumatoid flare affects joints and fibrous tissue, but the musculoskeletal symptoms of chronic hypercortisonism are more diffuse and generalized, being referable more to muscles than to joints and fibrous tissue, and are associated with signs of cutaneous and subcutaneous hypersensitivity and hyperalgesia.

Rest may make the patient with rheumatoid arthritis worse temporarily, but rest benefits the rheumatoid patients with chronic hypercortisonism whose aching is cyclically related to fatigue. Physical therapy or salicylates are helpful to patients with a rheumatoid flare but do not adequately relieve the symptoms of chronic hormonal overdosage.

The sedimentation rate may be increased in chronic hypercortisonism as well as in a flare of rheumatoid arthritis, and thus it is not of much differential value in this instance.

A patient's remarks to the effect that his arthritis "is getting worse" or "coming back" require careful analysis. A flare of rheumatoid arthritis may occasionally occur while chronic hypercortisonism is present, but detailed observations are needed to permit an accurate decision with regard to the indications for either lowering or raising temporarily the hormonal dosage.[20, 21]

Diffuse Mesenchymal Reactions

When diffuse mesenchymal reactions develop in rheumatoid patients with chronic hypercortisonism, they simulate certain features of systemic lupus erythematosus[21-28] or periarteritis nodosa.[14, 21, 23-29] The incidence of features simulating these diseases was shown in a study of three comparable groups of patients with rheumatoid arthritis who came to the Mayo Clinic for diagnosis and treatment in a period of two and one-half years between 1951 and 1954 (table 1).[30] One group consisted of 105 patients with rheumatoid arthritis who had not had hormonal therapy. A second group was composed of 166 patients who had had hormonal treatment but had not had signs or symptoms of chronic hormonal overdosage. The third group consisted of 128 patients who presented features of chronic hormonal overdosage.

In the third group were 18 patients (14%) whose mesenchymal reaction was characterized by signs and symptoms simulating those of systemic lupus erythematosus, including the presence of L.E. cells in plasma or bone marrow, or both. Of these 18 patients, more than 50% had fever in excess of 100° to 101° F. at some time during the reaction, and 50% had nephritis. Transfusion reactions also had occurred in 33%, leukopenia in 28%, encephalopathy in 22%, serositis in 17%, purpura in 17%, sensitivity to exposure to sunlight in 11%, pneumonitis in 11%, false-positive results of serologic tests on the blood in 7%, and phlebitis in 7% of these 18 patients.

TABLE 1

Incidence of Various Signs and Symptoms in Patients with Rheumatoid Arthritis with and without Manifestations of Hypercortisonism

Sign	Rheumatoid Arthritis		
	Hormonal Therapy		No Hormonal Therapy, % of 105 Patients
	Chronic Hypercortisonism, % of 128 Patients	No Chronic Hypercortisonism, % of 166 Patients	
L.E. cells in blood or marrow	14	5	5
Fever	42	41	33
Nephritis	28	20	30
Transfusion reaction	35	7	9
Leukopenia	17	7	6
Pneumonitis	13	11	10
Encephalopathy	9	2	1
Serositis	8	9	9
Phlebitis	8	4	2
Sensitivity to sun	7	5	10
Purpura	5	0	14
False-positive serologic tests in blood	3	5	7

Severe mesenchymal reactions simulating those of periarteritis nodosa were observed in five patients who had peripheral neuritis, diffuse panarteritis histologically characteristic of periarteritis nodosa (figure 1), vascular occlusion, cutaneous ulcers, nephritis, fever, leukocytosis and hypertension.

The severity of these various reactions, if not their incidence, was more pronounced than in either of the control groups observed during the same period.

The question may be raised as to whether the rheumatoid patient who has a diffuse mesenchymal reaction simulating systemic lupus erythematosus from chronic hormonal overdosage actually has systemic lupus erythematosus rather than rheumatoid arthritis. Although this is a possibility which requires further study, at least some significant clinical and laboratory differences in the mesenchymal reactions of the two conditions can be recognized at this time by repeated detailed observations such as have been described. These differences are important from the standpoint of both prognosis and treatment. Also, when the effects of chronic hormonal overdosage, which simulate systemic lupus erythematosus, are eliminated before irreversible changes have occurred, the rheumatoid patient generally reverts to a type of reaction more typically compatible with the course of rheumatoid arthritis than with the course of systemic lupus erythematosus as it is now recognized.

The mesenchymal tissues of the patient with rheumatoid arthritis who has severe mesenchymal reactions during administration of chronically excessive doses of adrenocortical hormones seem to be "disarmed" in some manner by the chronic hormonal overdosage. This results in greater vul-

nerability to various and oftentimes severe mesenchymal reactions than would have been anticipated without the excessive hormonal therapy. In some instances the severe mesenchymal reactions have been irreversible and death has resulted.[2, 18, 20, 24–26, 29] In any event, the seriousness of chronic hormonal overdosage is increased by the development of severe mesenchymal reactions.

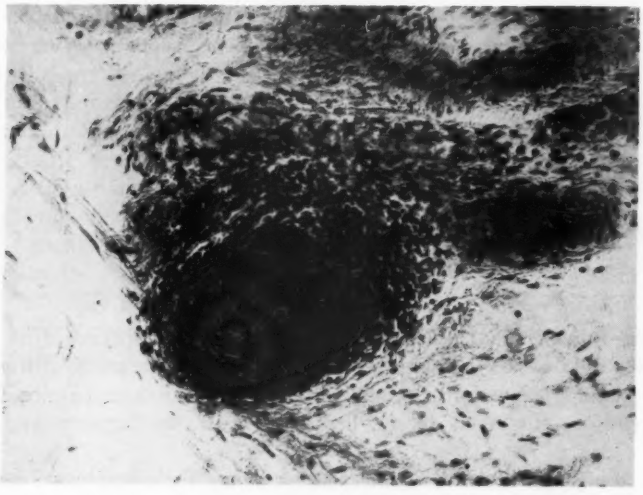

FIG. 1. Section from gastrocnemius muscle of a man, aged 56 years, showing diffuse panarteritis with occlusion and adventitial inflammatory reaction histologically characteristic of periarteritis nodosa (hematoxylin and eosin; × 150). The patient had had rheumatoid arthritis for 17 years, cortisone therapy for four years. Chronic hypercortisonism developed with signs of peripheral neuritis, pneumonitis, cutaneous ulcer, fever, weakness, muscular and articular aching, depression, hypersensitivity and hypertension.

TREATMENT OF CHRONIC HORMONAL OVERDOSAGE

The problem of relieving a patient with chronic hypercortisonism is much more complicated than simply stopping hormonal therapy, since this may result merely in exchanging the undesirable effects of exogenous chronic hypercortisonism for the equally unpleasant and distressing effects of endogenous hypocorticalism and its diffuse mesenchymal reactions. Because the effects of the hormones are insufficiently understood in terms of the interaction of the various glands and biochemical changes occurring in various tissues, treatment of chronic hypercortisonism is at present only partially satisfactory.

Coöperative Patient. The first requirement for the most satisfactory management of problems related to chronic hormonal overdosage is to obtain the patient's coöperation and confidence. This is facilitated by helping the patient to recognize the symptoms and signs attributable to hormonal overdosage and to understand the advisability of correcting the condition.

Patients sometimes worry about their increased weight, acne, hirsutism, irregular menses, emotional instability, fatigability and musculoskeletal aching due to hormonal overdosage, but often their main concern is that correction of hypercortisonism will deprive them of definite antirheumatic relief. Patients need also to understand that the period of treatment required to correct the effects of chronic hypercortisonism is likely to be long and uncomfortable, and that temporarily distressing reactions may occur during this period. Relief of the effects of chronic hormonal overdosage, however, need not result in increased activity of the inflammatory reactions of the rheumatoid arthritis. Actually, patients may expect to feel better after the reactions of overdosage have subsided than during the existence of symptoms of the overdosage.

Many patients with undesirable effects of chronic hormonal overdosage are anxious to be relieved but do not realize that this can be accomplished satisfactorily.

Extra Rest. The second requirement for optimal benefits from treatment is for extra physical and mental rest and relaxation. Generally, adult patients with rheumatoid arthritis who have symptoms of chronic hormonal overdosage need at least—and often more than—12 to 14 hours of sleep and rest during each 24-hour period. Because of their short endurance and tendency toward increase of symptoms with fatigue, frequent rest periods during the daytime hours are advisable in addition to the resting hours at night.

When effects of chronic hormonal overdosage are severe, treatment may be facilitated by the extra rest in bed and additional medical supervision accomplished by hospitalization. When the symptoms are only mild or moderate, extra rest and confinement at home may be adequate. The advantage of increased rest in bed may be especially noticeable when, as a result of excessive hormonal dosage, rheumatoid patients have been more physically active than their affected or damaged joints should be expected to tolerate.

Adjustments of Dosage. Treatment of chronic hormonal overdosage is facilitated by gradual, slow, small reductions of dosage (figure 2). In the early stages of reduction, and especially when hormonal doses have been large, initial decreases of 5 to 10 mg. of cortisone or 1 to 2.5 mg. of prednisone or the appropriate equivalent doses for other related hormonal preparations may be possible as often as every three to seven days. However, when, from previous reductions, patients begin to experience temporary increases in rheumatoid symptoms simulating rheumatoid flares, decreases of only 1 to 2.5 mg. or occasionally 5 mg. of cortisone or 0.5 to 1 mg. of prednisone may be possible. The intervals between reductions in such instances may vary from a few days to several weeks at each attempted reduction. The mesenchymal tissues of a rheumatoid patient with chronic hormonal overdosage apparently need to become adequately adjusted to each new dose level before another reduction is attempted.

Adjustment of dosage is further facilitated by regular, equally spaced administration of daily doses, usually every six or eight hours. The total dose for 24 hours should be divided as evenly as practical for each patient throughout this period.

Whenever significant signs or symptoms of adrenocortical insufficiency develop during attempts to reduce the hormonal dosage, administration of cortisone, hydrocortisone or their effective analogues may need to be con-

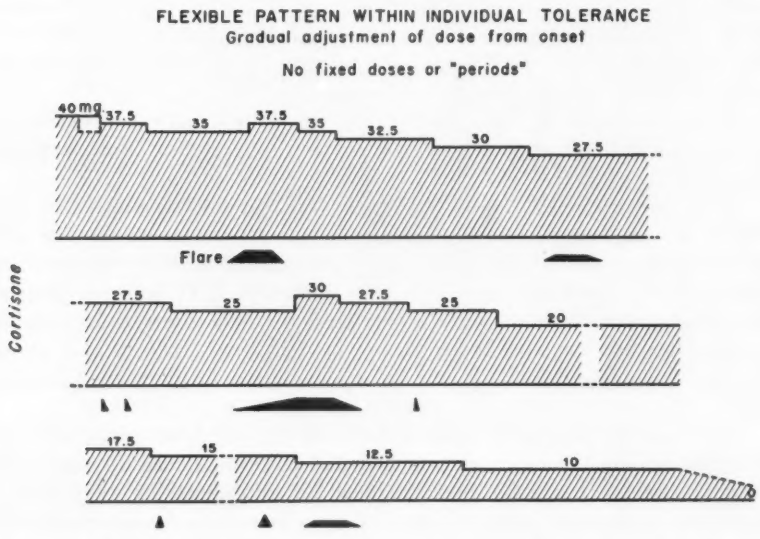

FIG. 2. Flexible pattern of hormonal dosage for rheumatoid arthritis. Initial as well as maintenance doses are kept within the anticipated tolerance of the patient. This diagram illustrates the administration of cortisone to a man initially given 40 mg. daily. First dotted lines in the shaded area show a prompt decrease in dosage which may be indicated if effects of initial dose are excessive. Other dotted lines bordering the shaded area indicate elapse of time.

Decreases of 2.5 to 5 mg. at a time are made in accordance with the patient's progress. Extent, severity and duration of flares shown by solid triangles and trapezoids help determine varying need for adjustment of dosage. With this program, hormonal therapy may gradually be successfully discontinued and hypercortisonism avoided.

tinued in doses equivalent to 20 to 30 mg. of cortisone daily for varying periods of weeks or months. Subsequent reductions from this level are thus deferred and undertaken later very gradually and slowly. Some transient but diffuse mesenchymal reactions may require temporary increases in hormonal dosage, even though signs of hypercortisonism are still present. Other diffuse mesenchymal reactions may subside if further reductions in dosage are only temporarily delayed and other appropriate therapeutic measures used.

It is preferable, when possible, to decrease the dosage slowly and then completely discontinue hormonal therapy for whatever period is required to eliminate all recognizable effects of overdosage. This may be for several months or longer. If further hormonal therapy is then required to control active inflammatory reactions of the rheumatoid arthritis, such treatment may be more effectively reinstituted at low, tolerable dosages after the effects of previous overdosage have disappeared.

Use of corticotropin, hydrocortisone, prednisone or prednisolone, either as alternatives to or concomitantly with cortisone, has not shortened the time required for recovery from chronic overdosage.

Successful reduction of the dosage is essential for subsidence of symptoms and signs of chronic hormonal overdosage in patients with rheumatoid arthritis.

Additional Measures of Limited Value. Other treatment which may be useful, although of limited value, in the correction of effects of hormonal overdosage includes use of salicylates for their analgesic, antipyretic and anti-inflammatory effects. Approximately 2 to 4 gm. a day may be given in divided doses to adults. But, as previously noted, salicylates may not provide the desired degree of relief, since the muscular and articular aching of chronic hypercortisonism may be less the result of rheumatoid inflammation than of some other abnormality of biochemical or other origin.

Physical therapy, even when mild, may be temporarily more fatiguing than the patient with chronic hypercortisonism can comfortably tolerate. But maintenance of optimal articular and muscular function is as desirable during hypercortisonism as at other times.

The maintenance of an optimal nutritional status may necessitate restriction of caloric intake and use of vitamin supplements in many instances. Extra supplemental doses of ascorbic acid up to 1 gm. daily occasionally have been helpful in the management of chronic hypercortisonism. Supplemental use of the constituents of the vitamin B complex has been tried. Deficiency of pantothenic acid, according to Bean and Hodges,[31] may simulate adrenocortical insufficiency; deficiency of nicotinic acid also results in certain emotional features [32] similar to those seen in patients with chronic hypercortisonism.

Use of amphetamine sulfate has had little or no effect on the emotional instability and fatigue of rheumatoid patients with chronic hypercortisonism. Chlorpromazine, on the other hand, has been of some help for these patients.

Attempts to control various features of hypercortisonism by supplemental use of potassium salts, reduced intake of sodium, use of thyroid extracts or estrogens and androgens, although seemingly rational, have not obviated the necessity of reducing the dosage of the adrenocortical hormones to tolerable levels. Furthermore, when the hormonal dosage is sufficiently reduced, these supplements are not required.

Prevention of Acute Adrenocortical Insufficiency. Patients with chronic hypercortisonism are susceptible to the effects of acute adrenocortical insufficiency resulting from the stress of major operations, trauma or severe infection.[33, 34] Hence, cortisone or other hormones should certainly not be stopped or decreased, and in many instances doses need to be appreciably increased to protect the patient during such a period. The intramuscular administration of approximately 600 mg. of cortisone in the 48 hours before elective operation and of approximately 200 mg. in the first 48 hours after operation, or 100 to 400 mg. of hydrocortisone prepared for intravenous use if necessary during the emergent stressful period, has been effective, at least empirically. Based on corticosteroid excretion of patients receiving

INFORMATIONAL POCKET CARD

Attention: Hospital or Police Physicians
Name_____
Address_____
has received __(Cortisone or ACTH)_____
for __(Rheumatoid Arthritis). This treatment was
started __(Date)__ and _(Continues to date).
Daily dose is_____mg. ____(Date)____.
_____mg. _____
Over

In case of accident or shock additional amounts may be required immediately to prevent circulatory collapse from acute adrenocortical insufficiency.
Refer to J.A.M.A., 1953: Vol.152,p.119, (May 9); or p. 1509, (Aug. 15). OR CALL--
Dr.____(Home Physician)___Phone_____
or (Address)
Dr._____Phone_____
Over

FIG. 3. Informational pocket card useful for patients who are receiving or have received long-term therapy with adrenocortical hormones. Any patient who has had hypercortisonism should have information available to emergency physicians and police officers regarding the possible need of supplementary hormonal therapy in the event of severe stress with adrenocortical insufficiency occurring during or possibly within six to 12 months or longer after subsidence of the hypercortisonism.

adrenocortical hormones [8] and of normal patients subjected to operation,[35] these amounts may supply about as much exogenous cortisone or hydrocortisone as the patient's own adrenal cortices would produce in response to the stress if not temporarily suppressed.[34]

Rheumatoid and other patients given cortisone or related hormones should be advised to carry a pocket card on which the pertinent information regarding their hormonal treatment is immediately available in the event of emergency (figure 3). Further experience is needed to determine the duration of reduced endogenous adrenocortical and anterior pituitary hormonal response of hormonally treated patients exposed to the effects of

stress. In some instances at least, this period apparently may extend for a year or more after administration of adrenocortical hormones or corticotropin has been discontinued.

Prevention of Hypercortisonism

Since treatment of chronic hypercortisonism is at best slow, difficult and perhaps inadequate, owing to limited understanding of the biochemical and other mechanisms of its development, prevention of hypercortisonism is important.

Measures include appropriate selection of patients and a stage of the disease suitable for hormonal therapy, acceptance by patient and physician of improvement compatible with safe dosage of the hormone, regular times of administration and usually regular divisions of doses of the hormone throughout the 24 hours, individualization of dosage at all times, and other treatment as indicated to supplement the hormonal therapy.

Table 2

Currently Estimated, Maximally Tolerated Daily Doses for Long-term Hormonal Therapy in Rheumatoid Arthritis

Group	Cortisone, mg.	Hydrocortisone, mg.	Prednisone or Prednisolone, mg.
Children	<10	<7.5	<2
Adolescents	10–15	7.5–10	2–3
Postmenopausal women	20–30	15–25	3.5–5
Premenopausal women	30–37.5	25–30	5–6.5
Adult men	37.5–50	30–40	6.5–9

The maximally tolerated, total daily doses of the hormones vary with the age and sex of the patient, and as experience with long-term hormonal therapy has increased, physicians' estimates of this dose have been lowered.

Currently recognized limits of dosage needed to avoid chronic hypercortisonism in patients with rheumatoid arthritis are summarized in table 2. As illustrated with use of cortisone, these doses for children are less than 10 mg. daily, for adolescents 10 to 15 mg. daily, for postmenopausal women 20 to 30 mg. daily, for premenopausal women 30 to 37.5 mg. daily, and for adult men 37.5 to 50 mg. daily. Proportionately lower doses apply for the use of hydrocortisone, prednisone, prednisolone or corticotropin. Occasionally a patient may tolerate doses that are slightly more or less than these amounts. It is desirable to avoid excessive doses of cortisone or related steroids or corticotropin at the start of as well as during long-term hormonal treatment.

Summary

Excessive exogenous hormonal dosage with cortisone, hydrocortisone, prednisone, prednisolone or corticotropin may result in either acute (short-term) or chronic (prolonged) hypercortisonism.

Chronic hypercortisonism in rheumatoid patients is characterized by the cyclic and usually associated occurrence of increased fatigability, significant emotional instability and generalized muscular and articular aching, in addition to the other more commonly recognized signs of hypercortisonism. Diffuse mesenchymal reactions simulating systemic lupus erythematosus or periarteritis nodosa also may develop. These diffuse mesenchymal reactions are serious and may be fatal complications of chronic hormonal overdosage but do not reflect the degree of underlying rheumatoid activity, which may or may not be minimal after the rheumatoid patient recovers from the effects of chronic hypercortisonism.

When chronic hypercortisonism has occurred in rheumatoid patients, dosage of exogenous hormones needs to be gradually and slowly reduced in conjunction with other treatment until the signs and symptoms of excess dosage have disappeared. When reductions of dosage have been too rapid, a flare of the rheumatoid arthritis or other mesenchymal reaction may develop. If this occurs, the dosage may need to be temporarily increased and thereafter reduced more slowly. In other instances, reversible stages of diffuse mesenchymal reactions occurring in the course of chronic hormonal overdosage may be controlled by temporarily deferring reduction of the hormonal dosage to the desired level. In some patients, hormonal therapy ultimately may need to be discontinued for several months or longer to permit complete disappearance of the signs of hypercortisonism. When signs and symptoms of hypercortisonism have been eliminated, small doses of exogenous hormones within anticipated limits of tolerance for the patient's age and sex may be used satisfactorily in long-term hormonal therapy if needed.

Short periods of increased doses of adrenocortical hormones may be needed for those patients subjected to the added stress of surgical procedures, severe trauma or infections while still receiving hormonal therapy, or who have had signs of hypercortisonism in the six to 12 or more months preceding such stress.

The usefulness of these hormones for patients with rheumatoid arthritis is not judged by reactions developing as a result of overdosage. Optimally tolerated doses of cortisone or its effective analogues or corticotropin are potent and valuable therapeutic agents, despite the effects of chronic hormonal overdosage in patients with rheumatoid arthritis. However, in the long-term treatment of rheumatoid arthritis, dosages of exogenous adrenocortical hormones or corticotropin that result in chronic hypercortisonism are not advantageous and should be avoided.

SUMMARIO IN INTERLINGUA

Excessive dosages exogene de preparatos hormonal del typo de cortisona, hydrocortisona, prednisona, prednisolona, o corticotropina pote resultar in acute (i.e. non-prolongate) o chronic (i.e. prolongate) hypercortisonismo.

Chronic hypercortisonismo in patientes rheumatoide es characterisate per cyclic e usualmente associate occurrentias de augmentate fatigabilitate, significative instabilitate emotional, e generalisate dolores muscular e articular in ultra del plus communmente recognoscite signos de hypercortisonismo. Pote etiam disveloppar se diffuse reactiones mesenchymal que simula systemic lupus erythematose o periarteritis nodose. Iste diffuse reactiones mesenchymal es serie. Illos es complicationes de chronic excessos de dosage hormonal que pote devenir letal. Illos non reflecte le grado del subjacente activitate rheumatoide, proque iste activitate pote haber grados minimal o non minimal post que le patiente rheumatoide se restabli ab le effectos de chronic hypercortisonismo.

Quando hypercortisonismo chronic ha occurrite in un patiente rheumatoide, le dosage del hormones exogene debe esser reducite gradual- e lentemente, in conformitate con altere aspectos del tractamento, usque le signos e symptomas del excessos de dosage ha disparite. Quando le reduction del dosage es troppo rapide, un recrudescentia de arthritis rheumatoide o de un altere reaction mesenchymal pote occurrer. In tal casos il es forsan necessari reaugmentar le dosage temporarimente e postea reducer lo plus lentemente. In altere casos, le occurrentia de reversibile stadios de diffuse reactiones mesenchymal in le curso de chronic hormonodosages excessive pote esser continite per le suspension temporari del reduction del dosage hormonal. In certe patientes il pote devenir necessari interrumper le therapia hormonal durante plure menses o mesmo plus pro effectuar le disparition complete del signos de hypercortisonismo. Post que le signos e symptomas de hypercortisonismo es eliminate, parve doses de hormones exogene—intra le expectate limites de toleration pro le etate e le sexo del patiente—pote esser usate satisfacentemente in un therapia hormonal a longe durantia, si un tal es requirite.

Breve periodos de augmentate doses de hormones adrenocortical es possibilemente necessari pro patientes qui es subjicite al stress additional de operationes chirurgic o de sever trauma o infection durante le curso de lor therapia hormonal o qui ha exhibite signos de hypercortisonismo in le curso del sex a 12 menses precedente tal stress.

Le valor de iste hormones in le tractamento de patientes con arthritis rheumatoide non debe esser judicate super le base del reactiones evocate per lor administration in doses excessive. Dosages de toleration optimal de cortisona o de su efficace analogos o de corticotropina es potente e preciose agentes therapeutic in le tractamento de patientes con arthritis rheumatoide in despecto del effectos de chronic dosage excessive. Tamen, in le prolongate therapia de arthritis rheumatoide, dosages de exogene hormones adrenocortical o de corticotropina que resulta in hypercortisonismo chronic es disavantageose e deberea esser evitate.

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GASTROINTESTINAL SYMPTOMS AS A CLUE TO THE DIAGNOSIS OF PRIMARY HYPERPARATHYROIDISM: A REVIEW OF 45 CASES *

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THE gastrointestinal symptoms of primary hyperparathyroidism have been noted repeatedly since the earliest clinical descriptions of the disease. The fourth confirmed case, reported by Boyd, Milgram and Stearns [1] in 1929, had periodic attacks of severe abdominal pain and vomiting occurring every three weeks for one year prior to parathyroidectomy, as well as constipation of five years' duration. These symptoms disappeared promptly after operation, and bowel function became normal. The first 115 reported cases of hyperparathyroidism were reviewed in 1934 by Gutman, Swenson and Parsons,[2] who pointed out the occurrence of such symptoms as nausea and vomiting, anorexia and epigastric pain. Subsequent clinical reviews [3, 4, 5, 6, 7, 8] and many individual case reports have mentioned gastrointestinal symptoms but in general have assigned very little diagnostic value to them.

In so-called "acute hyperparathyroidism" on the other hand, gastrointestinal symptoms have received considerable emphasis,[9-14] but this syndrome presents a rather distinct clinical picture. Waife [13] compared and contrasted the findings in acute and chronic hyperparathyroidism. He pointed out under "gastrointestinal manifestations" that in the acute form one finds "intractable vomiting, epigastric pain, constipation, occasional duodenal ulcer and gastric mucosa calcification," while in the more chronic form of the disease constipation may be present but the gastrointestinal symptoms are usually minimal. Snapper [8] has also described the "digestive syndrome" of hyperparathyroidism as a rare manifestation of the disease which is dependent upon extreme hypercalcemia.

In the more common or chronic form of primary hyperparathyroidism, gastrointestinal symptoms have been relegated to a minor rôle by the relatively greater importance of osseous and renal manifestations. This is quite understandable. Historically, a variety of skeletal symptoms and findings—generalized osteitis fibrosa, bone cysts and tumors, pathologic fractures and other skeletal distortions—were the earliest recognized indications of parathyroid overactivity. Even before Mandl's first successful parathyroidectomy in 1925,[15] a number of pathologists [16, 17, 18, 19, 20] had described an association between abnormalities of the skeleton and the para-

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thyroid glands. When the association had been clarified by Mandl and others [21, 22] skeletal changes became the principal clinical clue to the diagnosis of hyperparathyroidism.

In the early 1930's the renal manifestations of the disease—renal stones, nephrocalcinosis, polyuria and polydipsia—became more widely known. Albright and co-workers [23, 24] showed that renal stones were an important clue to the diagnosis of many cases of hyperparathyroidism. They suggested doing serum calcium and phosphorus determinations on all patients with urinary calculi. This practice has uncovered a number of otherwise unsuspected cases of hyperparathyroidism. Renal stones have indeed proved themselves the single most helpful clinical aid to early diagnosis of the disease.

If the osseous and renal manifestations of the disease are well known, what then is the diagnostic value of the more obscure gastrointestinal symptoms? The answer to this question lies in the particular need for the *early* diagnosis of hyperparathyroidism. The variety of skeletal abnormalities which may prove crippling and the disturbance of renal function which leads to the death of these patients [25] are both reversible—but reversible only if corrected before an ill-defined "point of no return." Until the physician has first suspected hyperparathyroidism on the basis of clinical clues, the diagnostic biochemical studies are seldom requested. To make matters more difficult, most of the early clinical clues are nonspecific and hardly suggestive of an uncommon disorder. The early bone symptoms are often vague pains, easily misinterpreted as "rheumatism" or "neuritis." Renal symptoms are not usually manifest until stone formation has occurred; and stones, if they do occur, may give symptoms either early or late in the over-all course of the disease. A few reports in the more recent literature [26, 27, 28] have stressed the diagnostic significance of the gastrointestinal symptoms of hyperparathyroidism. It is the purpose of this review to emphasize further the importance of gastrointestinal symptoms as additional nonspecific help in the earlier recognition of this cryptic disease.

Cases Studied

A study of the case records of the Presbyterian Hospital, New York, up to February, 1955, revealed 45 proved cases of primary hyperparathyroidism. A number of these cases have been reported previously to illustrate various aspects of the disorder.[2, 29, 25, 31]

Gastrointestinal Symptoms

Gastrointestinal symptoms were prominent enough in 16 of the 45 patients to be clinically significant. The case records of these 16 patients are briefly abstracted in the Appendix.

Vomiting without satisfactory explanation was part of the clinical picture presented by nine patients (cases 1, 2, 8, 15, 22, 29, 30, 31 and 39).

Cases 1, 8 and 29 had vomiting of relatively short duration before the diagnosis of hyperparathyroidism was made. Their vomiting was presumably associated with an acute exacerbation of the disease. Cases 2, 15 and 22, on the other hand, had unexplained episodes of vomiting for 18, seven and 15 years, respectively, before their hyperparathyroidism was recognized. Case 2 had a peptic ulcer which seemed a fairly reasonable explanation for his vomiting; unreasonable, however, was the fact that his gastrointestinal symptoms were improved by a bland diet but made worse by a Sippy diet. The latter, with its milk and alkali regimen, probably added to the patient's hypercalcemia and thus to the gastrointestinal symptoms it was supposed to ease. Case 39 had epigastric distress and vomiting for a number of years which were not relieved by gastroenterostomy.

Case 26 had an acute episode three years before parathyroidectomy which, in retrospect, appears to have been due to hyperparathyroidism. The unexplained anorexia and marked weight loss followed by renal stones should have been sufficient grounds to suspect the diagnosis at the earlier date. Cases 13 and 43 had unexplained upper abdominal complaints, together with marked constipation. This combination of upper and lower gastrointestinal symptoms, although seen quite commonly in patients with peptic ulcer, should suggest the possibility of hypercalcemia as its cause.

Cases 32 and 36 show how peptic ulcer may represent the earliest principal clue to the diagnosis of hyperparathyroidism.

Of the nine patients in this series in whom abdominal pain was recorded as a prominent symptom, four had demonstrable peptic ulcers. Their pain was epigastric in location and quite typical of ulcer pain. Two other patients without demonstrable ulcers had epigastric pain, two had diffuse abdominal pain, and one had right upper quadrant postprandial distress.

All these patients with gastrointestinal symptoms had other complaints or findings suggestive of hyperparathyroidism. In themselves, unexplained gastrointestinal symptoms are vague and meaningless. They may, however, serve as a stimulus to the physician to ask more searching questions about minimal genitourinary or skeletal symptoms, and to give more concern to the "lassitude of body and mind" [1] which has been noted in so many patients with hyperparathyroidism, and which may lead to the erroneous diagnosis of psychoneurosis.

Gastrointestinal Symptoms Following Parathyroidectomy

In 11 of these 16 patients gastrointestinal symptoms subsided promptly following parathyroidectomy. One patient (case 44) died before parathyroid exploration could be undertaken. Three patients (cases 30, 36 and 39) had further gastrointestinal symptoms after operation. Case 30 had some nausea and vomiting during her postoperative course in the hospital, but these symptoms cleared just prior to discharge. She had some abdominal pain six years after parathyroidectomy, at which time a hiatus

hernia was demonstrated. Although this may cast some doubt on the relationship of her earlier gastrointestinal symptoms to hypercalcemia, the relative subsidence of symptoms following parathyroidectomy seems convincing. Case 36 shows a patient's course following removal of one of two parathyroid adenomas, the second adenoma not being identified at the time of operation. Postoperatively the serum calcium fell to normal levels. Subsequent symptoms of vomiting and marked weakness, together with a rise of serum calcium to 13 mg.%, strongly suggested recurrent hyperparathyroidism. The patient died, presumably from a combination of renal failure and acute hyperparathyroidism, before his neck could be explored surgically again, and at autopsy a second parathyroid adenoma was found.

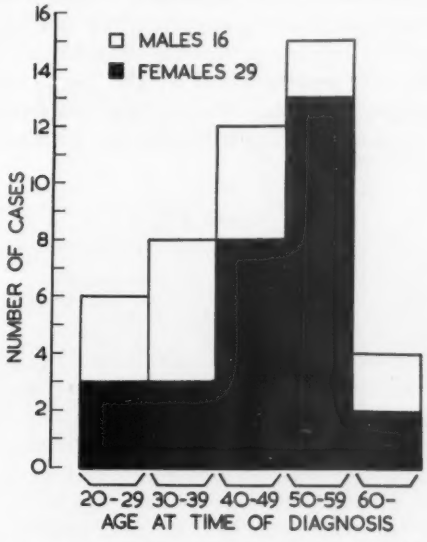

FIG. 1. Age and sex distribution of the 45 patients.

Case 39 had continued epigastric distress and vomiting following parathyroidectomy. Nine years after parathyroidectomy she had a partial gastrectomy because of bleeding from a large jejunal ulcer, and a year later she had a vagotomy because of hematemesis. Subsequently, high serum calcium and low serum phosphorus values have been found, and the patient's bones have not remineralized as well as they should have since her parathyroidectomy in 1943. Thus one wonders if the patient's gastrointestinal symptoms since her parathyroidectomy have been caused by a second parathyroid adenoma.

The symptoms of abdominal pain noted in nine cases were all promptly improved following parathyroidectomy, suggesting that they were in some way related to hyperparathyroidism.

Age and Sex Distribution

The age and sex distribution of the 45 patients under study is shown in figure 1. A predominance of females, though not so great as in most other series, is seen. Of interest is the fact that the incidence of the disease in females increases after the menopause. This was also found by Wilder and Howell [31] and by Norris [32] in their larger series. The age and sex distribution of the 16 patients with gastrointestinal symptoms parallels that of the over-all group.

Symptoms and Clinical Findings

Tables 1 and 2 summarize the symptoms and clinical and x-ray findings of the 16 patients with prominent gastrointestinal manifestations (referred to as the "G. I. Cases"), together with those of all 45 patients. Aside from the increased incidence of weakness and weight loss in the gastrointestinal cases, there is no striking difference between these two groups. The over-all findings, furthermore, are in keeping with what has been reported in previous reviews.[3, 4, 5, 6, 7, 23, 33, 34, 35, 36, 37, 38]

Table 1

Symptoms

	G.I. Cases (Expressed as percentages)	All Cases
A. *General*		
1. Weakness, easy fatigability	50	31
2. Weight loss (over 10 lbs. in last year)	25	11
B. *Urinary*		
1. Flank pain or renal colic	50	53
2. Nocturia or polyuria	31	33
3. Pyuria	0	11
4. Polydipsia	6	7
5. Gross hematuria	0	7
C. *Skeletal*		
1. Bone pain in lower extremities	44	62
2. Low back pain	25	27
3. Fractures	6	13
D. *Gastrointestinal*		
1. Constipation	31	29
2. Nausea and/or vomiting	56	20
3. Marked anorexia	25	16
4. Epigastric pain	38	13
5. Diffuse abdominal pain	13	4
6. Diarrhea	0	4
7. RUQ post prandial distress	6	2
E. *Neuropsychiatric*		
1. Severe headache	13	9
2. Pronounced emotional symptoms	6	7
3. Fainting spells	0	4
4. Numbness of feet	0	2

TABLE 2

Clinical and X-Ray Findings

	G.I. Cases (Expressed as percentages)	All Cases
A. *Urinary Tract*		
1. Stones	62	62
2. Nephrocalcinosis	19	18
B. *Skeletal*		
1. Osteitis fibrosa generalisata	88	76
2. Bone cysts	31	38
3. Pathologic fractures	13	18
4. Lamina dura absent	13	9
5. Bone tumors	6	4
6. Shortened phalanges	0	4
7. Narrowing of rib cage	0	4
8. Distorted pelvis	0	4
9. Collapsed vertebrae	0	4
10. Scoliosis (dorsal)	6	2
11. Destruction distal portion clavicle	0	2
12. Tibial bowing	0	2
No epulis, fish bone vertebra or herniation of nucleus pulposus		
C. *Gastrointestinal*		
1. Peptic ulcer	25	9
2. Hiatus hernia	6	2
3. Traction diverticulum of esophagus	0	2
4. Gastritis—leading to gastrectomy	6	2
5. Marked gastric atony noted on G.I. series	0	2
6. Melena	6	2

BIOCHEMICAL DATA

The significant biochemical data on these 45 patients are summarized in figures 2–5. The gastrointestinal cases, as indicated, have values of the same general order and distribution as those of the over-all group.

Representative preoperative serum calcium and phosphorus values are shown in figure 2. Cases 3, 24 and 29 have elevated phosphorus levels which are explained on the basis of renal insufficiency. Two of these patients died two years and the third four years following parathyroidectomy, all from renal failure. An elevated serum phosphorus in hyperparathyroidism at the time of operation is probably an indication that renal involvement has progressed beyond "the point of no return."

Figure 3 shows the relationship between alkaline phosphatase levels and the degree of bone disease as judged by interpretation of x-ray reports. The alkaline phosphatase was not significantly elevated in the presence of normal appearing bones by x-ray. As the x-ray evidence of bone disease increased, the alkaline phosphatase became less predictable.

Urinary calcium excretion over 24 hours while on a low calcium intake (100 to 150 mg. per day) was recorded in 15 patients. These determinations are represented in figure 4. As Albright and Reifenstein [3] have pointed out, the urinary calcium output while on a low calcium diet is usually over 150 mg. per day in hyperparathyroidism. Advanced renal disease

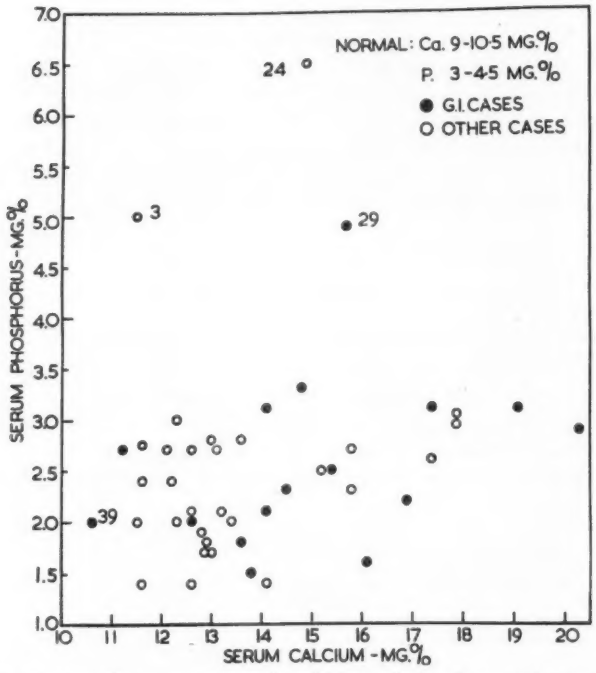

FIG. 2. Preoperative serum inorganic calcium and phosphorus determinations.

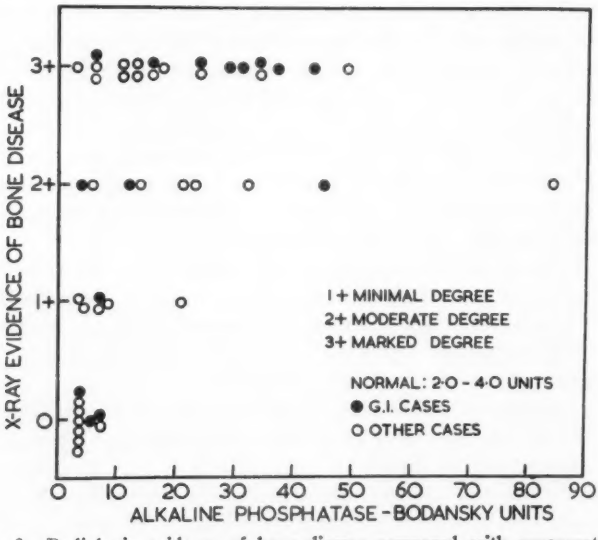

FIG. 3. Radiologic evidence of bone disease compared with preoperative alkaline phosphatase determinations.

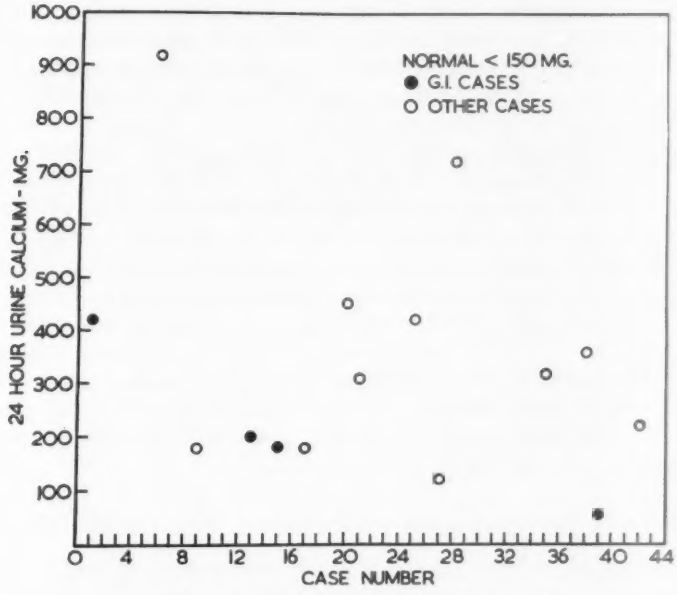

FIG. 4. Preoperative 24 hour urine calcium excretion after three to five days on a restricted calcium intake (100 to 150 mg. per day).

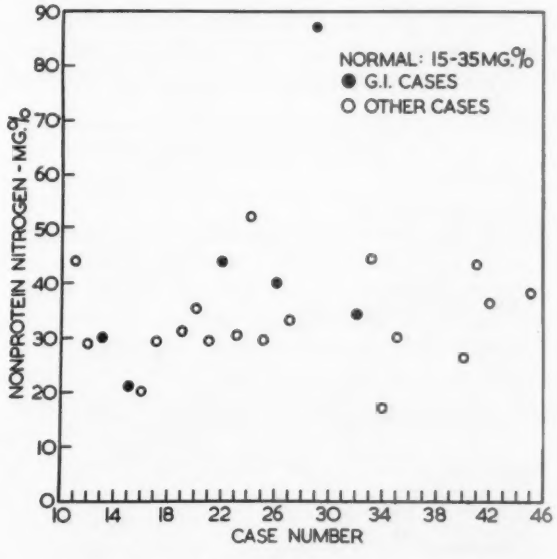

FIG. 5. Preoperative nonprotein nitrogen determinations on cases where recorded.

may reduce this figure. Cases 27 and 39, with no measurable renal disease, are exceptions to the usual finding. The low urinary calcium output in case 39 may be partly accounted for by the patient's serum calcium level of 10.6 mg.%; this serum calcium value is low for hyperparathyroidism, although just above the range of normal.

Figure 5 summarizes the recorded nonprotein nitrogen (N.P.N.) values. Three (cases 11, 24 and 29) of the seven patients (cases 11, 22, 24, 26, 29, 33 and 41) with a nonprotein nitrogen over 40 at the time of operation went into progressive renal failure following operation. Two patients (cases 22 and 26) were doing well, with normal nonprotein nitrogen, seven and eight years, respectively, following parathyroidectomy. Cases 33 and 41 have not had sufficient follow-up for any conclusions to be drawn.

In addition to the 24 patients with nonprotein nitrogens recorded, 13 other patients had blood urea nitrogen determinations done which were all normal. Thirty-three patients had total protein determinations recorded, and in 14 of these albumin: globulin ratios were also noted; all were essentially within normal limits.

Location and Pathology of Abnormal Parathyroid Glands

The location of the adenoma is of obvious importance to the surgeon. X-ray attempts at localization, either by swallow of thick barium or arteriography, are limited by the small size of many of these tumors. The majority of the adenomas in this series, as in previous reports,[39, 32] were in the lower glands (table 3), particularly if one assumes that the mediastinal tumors originate from aberrant lower parathyroids. In only one of these 45 cases was it necessary to split the sternum to remove the offending tumor. The upper mediastinal tumors could all be approached from the

Table 3

Location of Abnormal Parathyroids

	G.I. Cases	All Cases
Right lower parathyroid	5	13
Left lower parathyroid	4	13
Left upper parathyroid	3	10
Upper mediastinum	2	6
Left of sternum	0	1
Multiple small adenomas (lower)	0	1
Site not defined—adenocarcinoma	1	1
Site not recorded	1	1

Table 4

Pathology of Abnormal Parathyroids

	G.I. Cases	All Cases
Single adenoma	14	41
Two adenomas	0	1
Multiple small adenomas	0	1
Adenocarcinoma	1	1
Unknown	1	1

neck. The location of the abnormal parathyroids in the gastrointestinal cases followed a distribution pattern similar to that of all the cases.

The pathology of the parathyroid glands removed is recorded in table 4. Single adenomas were the cause of hyperparathyroidism in 41 of these 45 patients. This compares closely with Norris' series,[32] in which 93.8% of 322 cases had single adenomas. Tumor weight was recorded in 20 of the 45 cases, and ranged from 160 mg. to 36 gm. A rough correlation between tumor weight and level of serum calcium, as noted previously,[39, 40] was not found (figure 7). Adenoma weights were recorded in five of the 16 gastrointestinal cases. These weights ranged from 350 mg. to 36 gm., and there seemed no better correlation between adenoma weight and clinical picture than between adenoma weight and level of serum calcium.

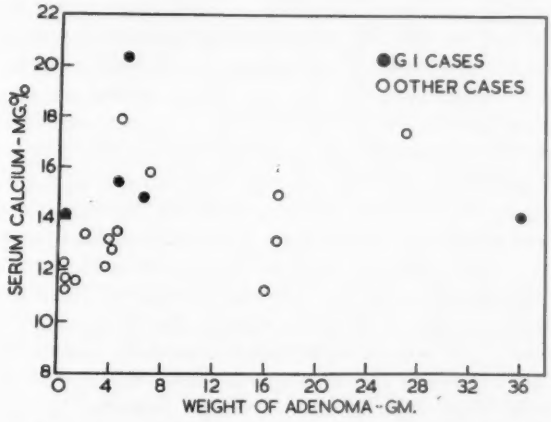

FIG. 6. Relationship between preoperative serum inorganic calcium and weight of parathyroid adenoma where recorded.

DISCUSSION

Hypercalcemia, which accounts for most of the clinical manifestations of hyperparathyroidism, is probably the principal cause of the gastrointestinal symptoms of this disease. In sympathetic ganglia, increased calcium ion concentration impedes transmission of afferent stimuli and diminishes efferent discharges in the presence of a constant amount of perfusing acetylcholine.[41] This effect, plus the effect of hypercalcemia on reducing neuromuscular excitability,[42] presumably leads to decreased tone of the gastrointestinal tract.

The marked constipation associated with hyperparathyroidism, probably even more frequent than this review indicates, is thought to be due to large bowel atony. Gastric atony presumably leads to the "dyspepsia," nausea and vomiting, although another, less well defined effect of hypercalcemia

may also contribute to these symptoms. Patients who are given intravenous calcium salts too rapidly often have immediate nausea and vomiting. This is particularly true if calcium chloride is given; calcium chloride, being a relatively acid salt, raises the ionized serum calcium more rapidly per unit injected than does calcium gluconate. The prompt appearance of vomiting that occurs in these patients may be quite nonspecific, but one wonders if it is not directly related to the sudden increase in serum calcium level.

Four of these 45 patients, or 8.8%, had peptic ulcers. This incidence is the same as that reported from the Massachusetts General Hospital, where 12 out of 137 patients with hyperparathyroidism were found to have peptic ulcer.[48] The relationship between these two diseases was discussed briefly in that report, and subsequently by Hellström[5] and *The Lancet*,[44] without any significant conclusions being reached. The mechanism by which hyperparathyroidism gives rise to a variety of abdominal pains is likewise not clear. One would suspect that such pains are associated with the functional bowel disturbance produced by hypercalcemia, but this is purely speculative.

It should be emphasized that gastrointestinal symptoms may arise when hypercalcemia occurs in conditions other than hyperparathyroidism. Thus when hypercalcemia is established in any given case, the diagnosis of hyperparathyroidism cannot be accepted until such causes of hypercalcemia as hypervitaminosis D, Boeck's sarcoid, multiple myeloma and metastatic malignancy are excluded. Other even less common conditions occasionally associated with hypercalcemia, such as the postadrenalectomy state, rapidly developing osteoporosis, and the syndrome resulting from prolonged and excessive intake of milk and alkali, should also be considered. The differential diagnosis of hypercalcemia, which has been well discussed before,[8] is not often difficult if its various possible causes are kept in mind.

The over-all clinical picture and findings presented by the 16 patients with significant gastrointestinal symptoms were quite consistent with those of the other cases. Why certain end organs are affected to a greater or lesser extent in different patients is as much a puzzle in hyperparathyroidism as in other endocrine disorders. Whether the puzzle will be solved in terms of more than one parathyroid hormone, multiple actions of a single hormone, or a variety of response inherent in the end organ remains to be seen. The immediate concern of the physician, however, is to recognize hyperparathyroidism despite its number of clever disguises, and to recognize it before the complications of the disease have become irreversible.

Gastrointestinal symptoms appear to represent a clue to the earlier recognition of some cases of hyperparathyroidism which has not been sufficiently emphasized. Unexplained episodes of nausea and vomiting, unexplained anorexia and weight loss, peptic ulcers which do not respond in the usual way to therapy, and a variety of unexplained abdominal pains should all lead to a consideration of hyperparathyroidism as a possible diagnosis. Hyperparathyroidism, which has been popularly thought of by medical men

as a "disease of stones and bones," might be recognized both earlier and more frequently if it were widely regarded as a "disease of stones, bones and abdominal groans."

Summary

The gastrointestinal symptoms of primary hyperparathyroidism as seen in 45 cases at the Presbyterian Hospital, New York, have been reviewed.

Sixteen of the 45 cases had gastrointestinal symptoms of clinical significance. The symptoms thought to be due to hypercalcemia consisted of nausea and vomiting, anorexia and weight loss, a variety of abdominal pains and marked constipation.

These gastrointestinal symptoms are meaningless in themselves. An awareness of their occurrence in hyperparathyroidism, however, may prove helpful in recognizing other nonspecific manifestations of a potentially reversible disease and thus lead to its earlier diagnosis.

Acknowledgment

The author is indebted to the members of the medical and surgical staff of the Presbyterian Hospital in New York for access to the records serving as the basis of this report, and to Dr. W. B. Stewart, of the Department of Pathology, Columbia University, for reviewing the histology of the parathyroid adenoma removed in case 39.

APPENDIX

Case Histories of 16 Patients with Prominent Gastrointestinal Symptoms

Case 1. A 34 year old male, admitted in 1933, had been vomiting three to four times per week during the four months before admission. He had had weight loss and weakness for two or three years, and polyuria and three to four times nocturia for two years. X-rays: calcification in horseshoe kidney, marked osteitis fibrosa generalisata (O.F.G.). Chemistry: calcium, 15.4; phosphorus, 2.5; alkaline phosphatase, 34.8; urine calcium, 432 mg. in 24 hours. A parathyroid adenoma was removed—right lower, 4.5 gm. The patient's gastrointestinal symptoms cleared and he did well for four years postoperatively, then slipped into renal failure and died in 1938. At post mortem, the stomach showed mucosal injection with prominent rugal pattern but no calcification.

Case 2. A 56 year old male was admitted in 1938 with epigastric pain of 10 years' duration. A gastric ulcer had been demonstrated in 1930 by x-ray. Pyloroplasty showed only rugal thickening. A kidney stone had been noted in 1930. He had had nausea and vomiting since 1920, which had persisted after gastric operation. Gastrointestinal symptoms became worse on a Sippy diet but improved on a bland diet. X-rays showed marked osteitis fibrosa generalisata. Chemistry: calcium, 19.1; phosphorus, 3.1; alkaline phosphatase, 23.0. An adenocarcinoma of the parathyroid was found. The patient did well for a short time postoperatively. There was a recurrent hyperparathyroidism in 1940; at operation a recurrent carcinoma was found. The patient died in 1944; there was no post mortem.

Case 8. A 21 year old female, admitted in 1944, had had episodes of vomiting for three months before admission, and weakness and pain in her legs and back for one year. X-rays showed multiple bone cysts and osteitis fibrosa generalisata. Chemistry: calcium, 14.5; phosphorus, 2.3; alkaline phosphatase, 37. A parathyroid

adenoma was removed, left lower. Her gastrointestinal symptoms cleared promptly, and she was doing well in 1948, when last seen.

Case 11. A 35 year old female, admitted in 1943, had had left costal margin pain radiating to her back and associated with meals for many years. She had had pain in her legs for two years. X-rays showed nephrocalcinosis with pyelonephritis, marked osteitis fibrosa generalisata, and a giant cell tumor of the femur. Chemistry: calcium, 14.1; phosphorus, 3.1; alkaline phosphatase, 14.2; blood urea nitrogen, 36. A parathyroid adenoma weighing 36 gm. was removed from the left upper mediastinum. Abdominal pain improved but her renal status gradually deteriorated. The patient was feeling fairly well in 1953 despite a blood urea nitrogen of 153 mg.%.

Case 13. A 63 year old female, admitted in 1936, had had right upper quadrant distress after meals for many years, marked constipation for 15 years, and pain and weakness of her legs for the last five years. X-rays showed moderate osteitis fibrosa generalisata. Chemistry: calcium, 12.5; phosphorus, 2.0; alkaline phosphatase, 11.6; urine calcium, 200 mg. in 24 hours. A parathyroid adenoma was removed from the left upper mediastinum. Her gastrointestinal symptoms cleared promptly, and she was doing well in 1946, when last seen.

Case 15. A 50 year old female, admitted in 1938, had had nausea and vomiting with diffuse abdominal pain for seven years, and renal stones known for four years. X-rays showed marked osteitis fibrosa generalisata with bone cysts. Chemistry: calcium, 11.2; phosphorus, 2.7; alkaline phosphatase, 30.3; nonprotein nitrogen 31; urine calcium, 170 mg. in 24 hours. A left lower parathyroid adenoma weighing 11 gm. was removed. Her symptoms cleared postoperatively. In 1941 the patient had recurrent episode of weakness, nausea, vomiting and abdominal pain, which subsided spontaneously; she was well in 1953, when last seen.

Case 22. A 49 year old female, admitted in 1947, had had occasional nausea and vomiting and persistent constipation for 15 years, renal colic for nine years, marked emotional disturbances, and progressive kyphoscoliosis. X-rays showed a normal gastrointestinal series, marked osteitis fibrosa generalisata, renal calculi and nephrocalcinosis. Chemistry: calcium, 14.8; phosphorus, 3.3; alkaline phosphatase 28.1; nonprotein nitrogen, 44; CO_2, 21.5. A right lower parathyroid adenoma weighing 6.5 gm. was removed. The patient had a stormy immediate postoperative course, with severe tetany, suspected pulmonary infarction and temporary renal shut-down. She subsequently did well, with relief of gastrointestinal symptoms. Her blood urea nitrogen in 1954 was 19.

Case 26. A 27 year old male was admitted in 1946. Three years before admission he had had an acute onset of fever, malaise and myalgia, followed by weakness, anorexia and a weight loss of 35 pounds in six weeks; 12 weeks later he passed three or four renal stones. He was diagnosed as a schizoid personality in 1944. His serum calcium was 14 at that time. He had fractured his right tibia one month before admission. X-rays showed osteitis fibrosa cystica and a pathologic fracture of the right femur; the lamina dura was absent. Chemistry: calcium, 20.3; phosphorus, 2.9; alkaline phosphatase, 5.9; nonprotein nitrogen, 40. A left upper parathyroid adenoma weighing 5.2 gm. was removed. A small area of papillary cancer of the thyroid was also seen on section. The thyroid was reëxplored surgically seven weeks later, but no further cancer was seen. The patient was doing well in 1954, when last seen.

Case 29. A 51 year old female, admitted in 1949, had had anorexia and vomiting for three months before admission. Three thousand I.U. of vitamin D daily for three weeks had been given three months before admission. She had had back pain, weakness and headache for three years. X-rays showed moderate osteitis fibrosa generalisata, calcification in the lungs, and nephrocalcinosis. Chemistry: calcium, 15.7; phosphorus, 4.9; alkaline phosphatase, 5.0; nonprotein nitrogen, 87. One

large parathyroid was removed but the tissue was lost before it could be examined microscopically. At operation other parathyroids were thought to be enlarged. The patient's serum calcium remained elevated postoperatively, with serum phosphorus normal to increased. The patient died in uremia in 1949 at Montefiore Hospital. At autopsy only two parathyroids were found, normal both grossly and histologically.

Case 30. A 37 year old female, admitted in 1948, had had unexplained vomiting one year before admission, but a normal gastrointestinal series. She had also had renal stones for three years before admission, abdominal pain, nausea and vomiting for three months before admission, and mild diabetes for one year, controlled by diet. X-rays showed minimal osteitis fibrosa generalisata. Chemistry: calcium, 14.1; phosphorus, 2.1; alkaline phosphatase 7.6. A left upper parathyroid adenoma weighing 0.35 gm. was removed. The patient did well following operation. She had abdominal pain in 1954, and a hiatus hernia was demonstrated. The pain subsided spontaneously, with the cause not clearly determined.

Case 31. A 57 year old female, admitted in 1949, had had vomiting and postprandial epigastric fullness for one year before admission. A gastrointestinal series had been negative. She had had a weight loss of 35 pounds in one year, and pain in her legs for two years. X-rays showed moderate osteitis fibrosa generalisata. Chemistry: calcium, 16.1; phosphorus, 1.6; alkaline phosphatase, 45. A left upper parathyroid adenoma was removed. The patient had a pulmonary infarct on her sixth postoperative day, but a good recovery despite this. She had gained from 100 pounds to 160 pounds by 1954, and had no further gastrointestinal symptoms.

Case 32. A 46 year old male, admitted in 1949, had had a duodenal ulcer demonstrated by gastrointestinal series in 1941, constipation shortly prior to admission, pain and weakness of his legs for two years, and severe frontal headaches for one year. X-rays showed moderate osteitis fibrosa generalisata, renal calculus, and an absent lamina dura. Chemistry: calcium, 16.9; phosphorus, 2.2; alkaline phosphatase, 12.1. A right lower parathyroid adenoma was removed. The patient had a smooth postoperative course, and his gastrointestinal symptoms cleared promptly. There was a marked general improvement three months later.

Case 36. A 69 year old male, admitted in 1952, had had a partial gastrectomy in 1941 for gastric ulcer, and polyuria, polydipsia and muscle weakness since the gastrectomy. Bilateral renal calculi had been noted nine months before admission. X-rays showed normal appearing bones. Chemistry: calcium, 13.8; phosphorus, 1.5; alkaline phosphatase, 3.4; blood urea nitrogen, 18. A right lower parathyroid adenoma was removed. Two weeks later stones were removed from the left ureter and the renal pelvis. Serum calcium at this time was down to 10.2. One month later the patient had vomiting, weakness and dysuria. The serum calcium was then back up to 13 mg. The patient died before his neck could be explored surgically again. Post mortem showed a second parathyroid adenoma, 4 cm. in diameter, just above the right clavicle; bilateral renal calculi with pyelonephritis; no osteitis.

Case 39. A 50 year old female, admitted in 1943, had had a gastroenterostomy for peptic ulcer four years before admission, with subsequent persistence of epigastric pain, vomiting and constipation. She had had no medical therapy. There had been a 20 pound weight loss and pain in the legs and low back during the two years before admission. X-rays showed marked osteitis fibrosa generalisata, a fracture of the neck of the left femur, and bilateral renal calculi. Chemistry: calcium, 10.6; phosphorus, 2.0; alkaline phosphatase, 43.1; total protein, 5.7; blood urea nitrogen, 8; urine calcium, 52 mg. in 24 hours. A left lower parathyroid adenoma was removed. Epigastric pain and vomiting continued, and was only poorly controlled by a strict ulcer diet. She had a partial gastrectomy nine years following parathyroidectomy for a large jejunal ulcer with bleeding, and a vagotomy one year later for hema-

temesis. Subsequently, the calcium was 11.4; phosphorus, 2.8; alkaline phosphatase, 4.2. X-rays showed failure to remineralize the bones since parathyroidectomy. The question of recurrent hyperparathyroidism was raised.

Case 43. A 58 year old male, admitted in 1952, had had upper gastrointestinal distress, anorexia, constipation and melena in 1949, a negative parathyroid exploration in 1951, and an abnormal gastrointestinal series and gastroscopy in March, 1952. His stomach had been explored surgically and found normal except for gastritis. He had had renal stones for 13 years, and left hip pain for three months before admission. X-rays showed normal appearing bones. Chemistry: calcium, 13.6; phosphorus, 1.8; alkaline phosphatase, 4.1; blood urea nitrogen, 17. A left lower parathyroid adenoma was removed. The patient had a smooth postoperative course. His gastrointestinal symptoms cleared, and he was doing well in 1955.

Case 44. A 56 year old female, admitted in 1950, had had unexplained anorexia for six months, a weight loss of 10 pounds in the last one or two months, constipation for a number of years, and low back and bilateral flank pain with associated frequency and nocturia for eight months. X-rays showed moderate osteitis fibrosa generalisata and bilateral renal calculi. Chemistry: calcium, 17.4; phosphorus, 3.1; alkaline phosphatase, 4.5; blood urea nitrogen, 11. The patient had left ureteral calculi removed, and on the eighth postoperative day her temperature spiked to 103° F., she went into shock and died. Post mortem showed an adenoma of the right lower parathyroid.

Summario in Interlingua

In un serie de 45 demonstrate casos de hyperparathyroidismo primari, vidite al Hospital Presbyterian de New York ante le mense de februario 1955, un total de 16 monstrava symptomas gastrointestinal de signification clinic. Iste symptomas consisteva de nausea e vomito, anorexia e perdita de peso, un varietate de dolores abdominal, e marcate grados de constipation. Ben que tal symptomas gastrointestinal es minus specific que le melio cognoscite manifestationes ossee e renal de hyperparathyroidismo, illos representa a vices un indicio possibile pro le establimento precoce del diagnose, e isto es multo importante in le presente morbo que es potentialmente reversibile. Es exprimite le opinion que iste symptomas gastrointestinal resulta de hypercalcemia. Altere conditiones associate con hypercalcemia debe esser excludite ante que le diagnose de hyperparathyroidismo pote esser establite.

Le symptomas e le constatationes clinic in general, le pertinente datos biochimic, e le pathologia del anormal glandulas parathyroide que esseva characteristic del casos hic presentate esseva comparabile al datos de previe reportos.

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EXERTIONAL DYSPNEA: A PRIMARY COMPLAINT IN UNUSUAL CASES OF PROGRESSIVE MUSCULAR ATROPHY AND AMYOTROPHIC LATERAL SCLEROSIS *

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Dyspnea is a symptom usually referable to disorders of the heart or lungs. Despite this frequent association, it is generally known that abnormalities of other systems may lead to respiratory disability. The muscles of the thoracic wall and diaphragm, by their bellows action, form the respiratory pump. Proper function of this pump is a prerequisite of normal pulmonary ventilation. Disturbance of the muscles of respiration is frequently seen in patients with poliomyelitis.[1, 2] The dramatic onset and clinical features of most cases of poliomyelitis usually allow for a prompt and correct diagnosis. In contrast, the more chronic neuromuscular disorders involving the muscles of respiration may, by their insidious onset and progress, simulate certain pulmonary or cardiac conditions and thus lead to perplexing problems in differential diagnosis. Progressive muscular atrophy and amyotrophic lateral sclerosis are two apparently related conditions which may mimic chronic cardiac or pulmonary insufficiency if the early symptom is exertional dyspnea.

Progressive muscular atrophy characteristically begins with weakness and wasting of certain striated muscles, most commonly the small muscles of the hand or shoulder. This wasting progresses fairly symmetrically, involving all striated musculature except the extraocular muscles. The atrophy and weakness are associated with muscle fasciculation. In amyotrophic lateral sclerosis spasticity occurs concomitantly with the atrophy, usually in the lower extremities, and is associated with hyperreflexia and the Babinski sign. Examination of the sensory system reveals no abnormality, nor is there evidence of impairment of mental function. Terminally, the spasticity becomes less pronounced, and eventually the atrophic changes in the musculature leave the patient with a flaccid type of paralysis. Late or terminal respiratory complications of aspiration pneumonia and pul-

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monary disability frequently occur, but they usually are not prominent features of the earlier phases of these disorders.

A number of cases have come to our attention in recent years indicating that these chronic neuromuscular disorders may initially present the symptoms of respiratory difficulty. When the more classic signs of atrophy of the muscles of the hands have not yet developed or are masked, this may pose a most difficult diagnostic problem.

The purpose of this paper is to report on three patients who were referred to the Mayo Clinic because of respiratory complaints and who were found to have primary muscular atrophy or amyotrophic lateral sclerosis but no demonstrable primary bronchopulmonary disorder. Studies of pulmonary function carried out in each of the three patients demonstrated certain abnormal features that were of diagnostic help (table 1). We elim-

TABLE 1

Results of Pulmonary-Function Tests in Three Patients with Neuromuscular Disease

Cases	Age, years	Vital capacity		Residual volume,* liters	Total lung capacity		Maximal breathing capacity		Maximal mid-expiratory flow[a]		7-min. alveolar nitrogen,† %	% arterial oxygen saturation	
		Liters	% of normal		Liters	% of normal	Liters per min.	% of normal	Liters per sec.	% of normal		Rest	Exercise
1	66	1.7	41	1.9	3.6	67	32	33	0.6	19	3.2	90	83
2	71	2.0	47	2.9	4.9	86	57	66	2.5	80	2.2	97	No fall
3	49	1.9	40	2.0	3.9	59	42	40	1.3	32	3.4	95	No fall

* Estimated normal is one third of predicted vital capacity. In old age, residual volume should not exceed 40% of total capacity.

† Alveolar nitrogen concentration after 7 minutes of oxygen inhalation. Normal values are 2.5% or less.

inated from consideration patients with a variety of other neurologic or muscular disorders and the early symptom of exertional dyspnea. We also excluded those patients with intrinsic pulmonary disease occurring coincidentally with neurologic or muscular disease.

CASE REPORTS

Case 1. A 66 year old heating inspector who came to the Mayo Clinic on March 17, 1954, complained of repeated attacks of upper abdominal pain that had occurred during the previous 18 months, that were colicky in nature, and that were relieved in four or five hours by a hypodermic injection. There was no vomiting, jaundice or acholic stool. Dull aching in the right upper quadrant occurred almost daily. He also complained of dyspnea on walking two blocks rapidly, but he could walk slowly for an indefinite period without experiencing dyspnea. There was no orthopnea. Since the onset of pain, he had reduced his weight from about 200 pounds to 164 pounds by dieting, but, on the basis of his height of 65 inches, he was still moderately obese.

Physical examination revealed a normal blood pressure. The pulse rate was 98 per minute and regular. Breath sounds were depressed over both pulmonary fields, but no râles were noted. The epigastrium seemed to retract instead of protrude with inspiration. There was no edema of the ankles or cardiac abnormality. Postero-anterior roentgenographic examination of the thorax revealed only torsion and calcification of the aorta. The pulmonary fields appeared normal. Cholecystographic examination showed cholelithiasis. Since exertional dyspnea was mild, studies of pulmonary function were not carried out prior to operation. The initial clinical impression was that there was a mild degree of pulmonary emphysema.

Cholecystectomy was carried out on March 24, since the attacks of colic in the right upper quadrant had become progressively more severe. On the third postoperative day the patient complained of orthopnea. Physical examination revealed transient râles posteriorly over the base of the left pulmonary field, but left lateral roentgenographic examination showed no abnormal pulmonary shadows. The dyspnea subsided only slightly, although the patient convalesced satisfactorily from the abdominal operation. After leaving the hospital on the ninth postoperative day he continued under medical observation.

On April 19, follow-up postero-anterior roentgenographic examination showed a shadow, 3 by 5 cm., in the base of the left lung compatible with a diagnosis of pneumonitis or its residue. Inspiration-expiration postero-anterior roentgenographic examination showed the diaphragmatic excursions to be apparently normal. On April 23, examination of the hands disclosed a suggestion of flattening of the thenar and hypothenar eminences, especially on the left. The diagnosis of progressive muscular atrophy was considered, even though the patient denied any muscular weakness or wasting. A few muscular fasciculations could be induced over the pectoral girdle by digital percussion. No pathologic reflexes could be elicited, which indicated lack of involvement of the corticospinal tract. Neurologic investigation, including electromyography, supported the clinical diagnosis.

By this time orthopnea had increased so that the patient sat in a chair to sleep. Fluoroscopy showed paradoxic motion of the diaphragm on the left and decreased excursion on the right. Studies of pulmonary function at this time revealed numerous abnormalities (table 1) considered to be consistent with weakness of respiratory muscles. By June 1 there was an increase in exercise tolerance. Roentgenographic examination showed only evidence of residual pleural thickening at the base of the left lung. The patient could walk four blocks without undue dyspnea. He returned to his job, which required almost continuous walking but no heavy lifting or similar stress. He could sleep comfortably lying on his right side but not consistently so on his left side or back.

Case 2. A 71 year old restaurateur came to the Mayo Clinic on July 25, 1954, with complaint of shortness of breath and tightness of the anterior part of the thorax when he walked only a half block. He had also noted epigastric distress and easy filling with meals. He had lost more than 35 pounds in the previous nine months. Because of moderate orthopnea he had used two pillows to sleep. His illness had forced him to give up his business.

Physical examination revealed a chronically ill man weighing 145 pounds. Expansion of the thorax was limited. The percussion note was hyperresonant. Breath sounds were diminished but expiration was not prolonged. The obvious evidence of weight loss and tympany over the upper part of the abdomen suggested to one examiner the possible presence of malignant disease of the gastrointestinal tract. The hyperresonance and dyspnea were considered possibly related to pulmonary emphysema.

The results of routine urinalysis, the determinations of hemoglobin, bilirubin and urea, and the leukocyte count were within normal limits. Roentgenographic examination showed some elevation of the diaphragm on the left; the heart and pulmonary fields appeared to be normal. Marked distention of the intestine with gas was noted on x-ray examination of the stomach and colon, but no intrinsic gastrointestinal lesions were noted.

The possibility of a neuromuscular disorder was suggested by the presence of some wasting of the interosseous muscles and of the thenar and hypothenar eminences of both hands. Testing of muscle strength showed slight weakness of the pectoral girdle and upper extremities. Deep tendon reflexes were somewhat exaggerated, and the Babinski sign was present on the left. The neurologic diagnosis was amyotrophic lateral sclerosis.

Studies of pulmonary function revealed changes compatible with weakness of the muscles of respiration rather than pronounced intrinsic pulmonary disease (table 1).

Case 3. A 49 year old paint inspector was referred to the Mayo Clinic on April 1, 1955, for investigation of "bronchial trouble." Symptoms of cough, production of sputum, exertional dyspnea, loss of weight and weakness had progressed during the previous two years. In January, 1953, a febrile illness diagnosed as bronchopneumonia had occurred that had required hospitalization. Over a two year period following the initial attack he had had similar episodes requiring hospitalization. Physical, bronchoscopic and bronchographic examinations three months prior to his coming to the clinic had been unrevealing. In 1944 he had worked for three months in a copper mine in Arizona but had had no respiratory symptoms while he was there or during the subsequent nine years that he had lived in the Midwest. On further questioning he admitted having had some dysphagia with choking spells since the onset of the recurrent pneumonia.

On physical examination there was evidence of weight loss. The muscles of the pectoral girdle, the thoracic wall, the back and, to a lesser extent, the pelvic girdle appeared to be wasted. There was no atrophy or weakness of the muscles of the hands.

Respiratory excursions of the thorax were somewhat diminished. Roentgenographic examination revealed a hazy, irregular, patchy density in the lower portion of the left pulmonary field compatible with a residue of aspiration pneumonitis.

The leukocyte count was 12,400 per cubic millimeter of blood, and the differential count revealed 14.5% lymphocytes, 8% monocytes, 75% neutrophils, 2% eosinophils and 0.5% basophils. Examination of two samples of sputum revealed no malignant cells. Smears and cultures of two samples of sputum demonstrated no acid-fast bacilli.

The results of pulmonary-function studies supported the clinical impression that the pulmonary symptoms were secondary to weak respiratory muscles. A contributing factor was the previous aspiration pneumonitis, apparently the result of paralysis of some of the pharyngeal muscles. Electromyography supported the clinical diagnosis of progressive muscular atrophy.

Comment

Patients in whom weakness of the muscles of respiration develops may present symptoms and signs suggesting the presence of pulmonary or cardiac disease. All the patients in this study had slowly progressing exertional dyspnea. The limitation of thoracic expansion and the depressed breath sounds, when noted, suggested an erroneous diagnosis of pulmonary em-

physema. All of these patients had varying degrees of weight loss, a feature often seen in cases of emphysema, even in the absence of intrinsic gastrointestinal abnormalities. One patient was still obese despite recent loss of weight. This masked muscular wasting, particularly in its early stages. When aspiration of oropharyngeal contents had occurred, the presence of cough further focused attention on the respiratory system. Two of the three patients noted orthopnea, which is not characteristic of pulmonary emphysema but which might have suggested the presence of cardiac insufficiency. The age of the patient was of no help in differential diagnosis, inasmuch as these neuromuscular disorders occurred at the same time of life as cardiac or pulmonary insufficiency frequently appears.

Some of the abnormalities noted in the tests of pulmonary function in these patients with neuromuscular disease may superficially resemble pul-

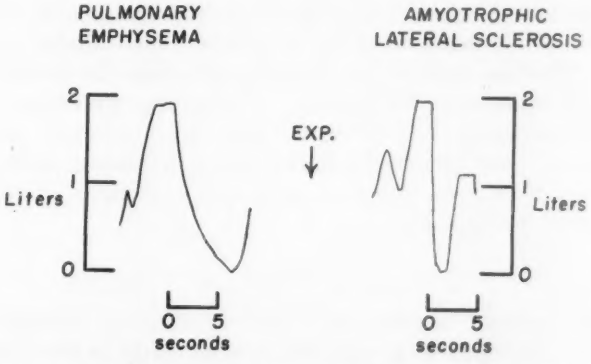

FIG. 1. Note the relatively rapid, straight, down stroke of expiration during the vital capacity effort of a patient with weakness of the muscles of respiration (case 2) (right), as compared with the typical spirogram seen in patients with severe emphysema with progressive slowing of expiration during the rapid vital capacity test (left).

monary emphysema. The vital capacity and maximal breathing capacity are reduced, and the ratio of residual volume to total capacity of the lungs is increased. Arterial hypoxemia may also be present. These similarities have been pointed out by Galdston.[4] Feltman and associates[5] reported similar changes in pulmonary function in a patient with muscular wasting of obscure origin. In our study we noted several features that contrast with those observed in patients with pulmonary emphysema. These included reduced values for total pulmonary capacity, and absence of significant increase of residual volume or functional residual capacity. Moderate increases of the latter two values were found in case 2, but may have represented the effects of old age and, with expiratory slowing absent, were not considered to indicate emphysematous changes. This is shown in the spirogram of a maximally rapid and deep expiration (figure 1). This type

of spirogram, in which the total volume is reduced but is expired at a relatively rapid and constant rate, resembles that often seen in patients with respiratory weakness following poliomyelitis. It is unlike the spirogram seen in emphysema, in which there is progressive expiratory slowing.

In two cases some degree of expiratory slowing was present in association with reduced maximal breathing capacities and abnormal nitrogen-washout indices. One patient also was hypoxemic. These may represent the combined effects of muscular weakness or asynergy, or both. Secondary intrapulmonary abnormalities arising from aspiration pneumonitis, bronchitis or residual fibrosis very likely contributed to the expiratory slowing. In each of the two patients with expiratory slowing there was evidence of recent or repeated episodes of bronchopulmonary irritation, which very likely resulted from aspiration of oropharyngeal contents.

The diagnosis in these atypical cases of primary muscular atrophy and amyotrophic lateral sclerosis was made initially on clinical information. Examination of the musculature for atrophy and fasciculation, and testing for muscle weakness and for the Babinski sign, gave the earliest clues as to the underlying cause of the dyspnea. Fluoroscopy, with special attention given to the movement of the thoracic wall and diaphragm, gave further evidence of the basis for labored breathing. Electromyographic examination and tests of pulmonary function supplied corroborative evidence in the cases presented in this study.

Summary

Primary muscular atrophy and amyotrophic lateral sclerosis may occasionally be associated with exertional dyspnea early in the course of the disease process before muscular atrophy and fasciculation in classic locations become evident. The clinician should consider these neurologic conditions in the differential diagnosis of dyspnea, especially if the cardiac and pulmonary findings are not compatible with the degree of respiratory disability.

Studies of pulmonary function may reveal abnormalities that suggest insufficiency of the muscles of respiration rather than primary intrinsic pulmonary disease.

Summario in Interlingua

Primari atrophia muscular e amyotrophic sclerosis lateral es a vices associate con dyspnea sub effortio in le prime phases del processo morbide, ante que atrophia muscular e fasciculation deveni evidente in le locos classic. Le clinico deberea prender iste conditiones neurologic in consideration in le diagnose differential de dyspnea, specialmente si le constationes cardiac e pulmonar non es compatibile con le grado del invaliditate respiratori.

Studios del function pulmonar revela possibilemente anormalitates que indica insufficientia del musculos de respiration plus tosto que un primari intrinsec morbo pulmonar.

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DIABETES MELLITUS AND CLINICAL RESEARCH: A STUDY OF INSULIN RESISTANCE*

By EWEN DOWNIE, M.D., F.R.C.P., F.R.A.C.P.,† *Melbourne, Australia*

"The secret—which is also the reward—of all learning lies in the passion for the search" (Quiller-Couch).

MR. President, distinguished guests and Fellows of the College, in thanking you for the invitation to deliver the Lilly Lecture for 1956 I recognize with pleasure the close professional relations which exist between our two countries and the compliment you have paid this day to Australian medicine. I am deeply conscious of my responsibility both to your College and to my colleagues at home.

It has been my good fortune to visit this country three times within the past 12 years. On the first occasion it was a remarkable experience to feel the intense sincerity and help from all whom I met, engaged as we were in the complex problems of war. The second occasion was last year, when I was concerned with another common problem: medical education. Again the same spirit of adventurous activity and of critical analysis, the same helpfulness and earnest desire to share experience were apparent wherever I went. And now you have done me the honor of asking me to address you on the occasion of this Annual Meeting.

This is an age of great achievements, and it has been the experience of us all to have witnessed extraordinary advances in the conquest of disease. These have occurred because of the ceaseless efforts of physicians and of scientists who have striven to explain the course and phenomena of ill health. Such close association is essential for the satisfactory prosecution of clinical research. So, in selecting my subject, I felt it appropriate that I should consider an aspect of diabetes mellitus which has perplexed me for many years and which exemplifies the value of a combined approach to clinical problems.

The isolation of insulin by Banting and Best occurred at a time when a static cellular philosophy had suggested that the islands of Langerhans were the seat of the specific diabetic disturbance, and that diabetes mellitus was a "unified entity rather than a disjointed symptom complex." [1] The past 30 years have added much to our knowledge and have changed this concept in a remarkable way. The recognition of complex homeostatic processes within the body, the great advances in biochemistry and in enzyme chemistry, and

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the growing importance of genetics have resulted in a dynamic concept of fluctuating influences which suggests a multiple etiology resembling the humoral philosophy of ancient Greece.

During this time the physician has witnessed great changes in the clinical course of diabetes mellitus. The dramatic improvement in health and well being of patients treated with insulin, the growth and maturity of the first generation of diabetic children ever known to the world, the recovery of patients from ketotic coma—once a prelude to certain death, the birth of children to diabetic mothers; these and many other things are commonplace observations in the present day. Likewise it has been our lot to witness, for reasons yet beyond our control, the relentless and inevitable progression of strange forms of vascular change in some patients who suffer diabetes for many years; and in the wealth of accurate and acute observations gathered through these years are other strange and rarer happenings: inexplicable remissions of the diabetic disorder,[2] and apparent worsening as estimated by the dosage and response to insulin. It is to this unusual and interesting phenomenon that I wish to direct attention.

The operation of total pancreatectomy for carcinoma of the human pancreas was first performed 12 years ago.[3] Since then, experience has taught that the insulin requirements of such patients are of the order of 40 to 50 units per day.[4] Patients who develop spontaneous diabetes often require more than this, but when control of hyperglycemia is established the dose, whatever it may be, usually remains constant within narrow limits for months or years. However, some previously well controlled patients pass into a phase where the dose required to maintain normoglycemia becomes inadequate, and control is regained only by the use of large doses, far in excess of those required by the depancreatized human being. For no good reason, it has been suggested that if a patient's daily dose of insulin exceeds 200 or 300 units he should be classified as "insulin resistant."[5] This curious clinical state sometimes runs a tumultuous course of many months, often with critical episodes of ketosis from which the patient is rescued with difficulty, and then quite gradually the insulin dose may be returned to its former figure. In other instances the state of resistance persists indefinitely. On rare occasions resistance appears in association with ketotic coma and seems to develop with alarming suddenness. No satisfactory explanation of this phenomenon is known. Smelo attempted to classify the causes of resistance on a functional basis.[6] Others have suggested that it is due to a delay in the absorption of insulin, to the presence of insulin antagonists in the blood stream, to overactivity of physiologic antagonists to insulin, to infections and liver disease, and to other less well defined causes.[7] This multiplicity of theories suggests that resistance is not a simple clinical entity.

In 1950 Bornstein and Trewhella, using A.D.H.A. rats, failed to demonstrate the presence of insulin in the serum of a group of insulin-resistant patients.[8] Recently Dr. Bornstein and I have studied another series of

such patients, many of whom have been under observation for months. In some, resistance has been transient, and at this time no insulin could be found in the serum. Later, when resistance had passed, ample insulin could be demonstrated in the serum. Furthermore, in other patients resistance was not associated with absence of circulating insulin as it developed when ample insulin was present in the blood stream. It is important to note that in no patient in this series was resistance associated with any clinical evidence of allergic reaction to insulin.

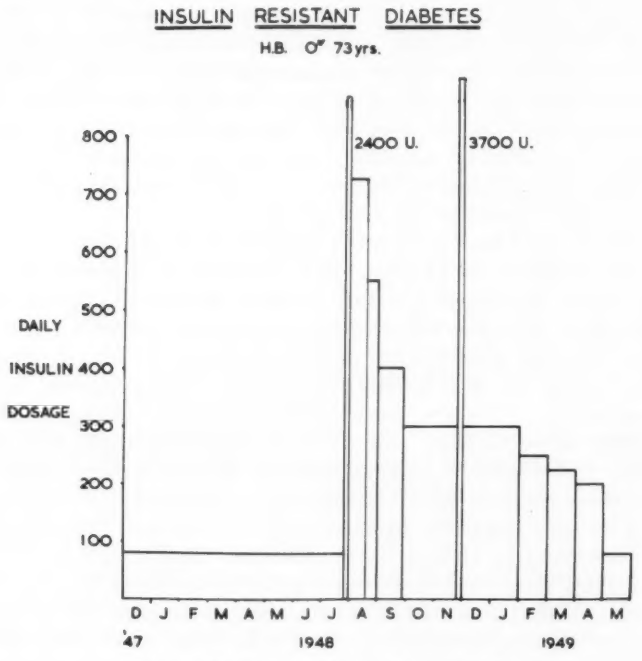

FIG. 1. Pattern of resistance in case H. B.

The following case records are typical examples of our experience:

CASE REPORTS

Case 1. In 1948 a 70 year old male developed classic symptoms of diabetes. He had never suffered from a serious illness, and had always been of spare build. When first seen he complained of rapid loss of weight and strength. He was easily brought under control with an appropriate diet and a daily dose of 40 units of mixed regular and protamine insulins. For the next eight months his condition was quite satisfactory, and then, for no obvious reason, he again became thirsty and lost weight. His daily insulin requirements rose rapidly, and within the next two months he required 700 units per day. His general state of health was not satisfactory; he failed to regain his weight, and twice within the next few months he

lapsed into severe ketotic coma. He recovered from these episodes with the use of large doses of insulin: 2,400 units were given in 24 hours on the first occasion, and 3,500 units on the second occasion. Following the second coma he gradually showed signs of regaining tolerance, and over the next six months his daily insulin requirement fell until it returned to the original figure of 40 units. This dose continued without variation for the next five years, and he enjoyed good health until his death from coronary occlusion at the age of 77.

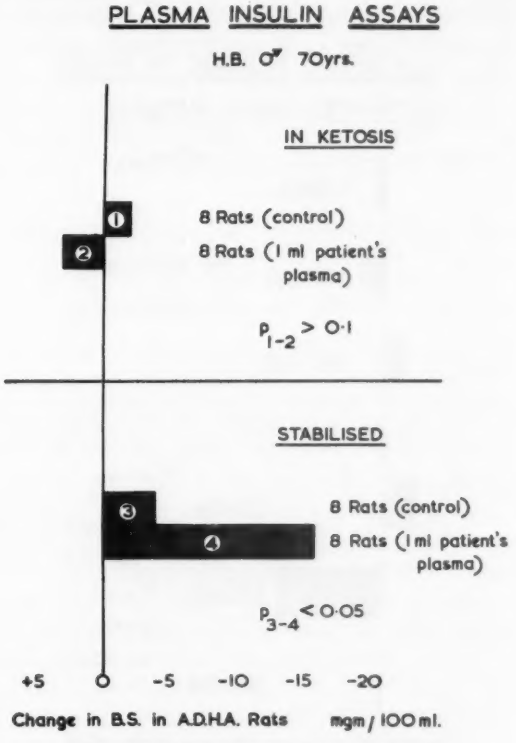

FIG. 2. Plasma insulin assays in case 1.

This is a familiar pattern of insulin resistance in many patients. It is of interest to realize that at the height of his resistance no circulating insulin could be demonstrated in his blood but later, when his resistance had passed, appreciable amounts were present.

Case 2. In 1948 I first saw a woman of 57 years, who stated that she had developed diabetes 18 years previously, while thyrotoxic. She had been treated surgically and had had no evidence of thyroid dysfunction since that time. She was of spare build, and complained of having had loss of weight and tiredness for some months before consulting me. She had never taken insulin. She was brought under control with an appropriate diet and a daily dose of 32 units of mixed regular and

protamine zinc insulins. For four months she remained well controlled and then gradually over the next six months her insulin requirements rose to 200 units per day. She then developed a severe ketotic coma, from which she recovered by the use of 3,500 units given over a period of 28 hours. Following this she required 600 units per day for a few weeks, during which the dose gradually fell to 140 units. Dr. Bornstein was unable to demonstrate any insulin in her crude plasma, and it was possible to transfer resistance to animals. For the next six months her insulin dosage varied between 140 and 250 units. At that time she again became ketotic, following an infection of the leg, and required 1,100 units in 24 hours. She left

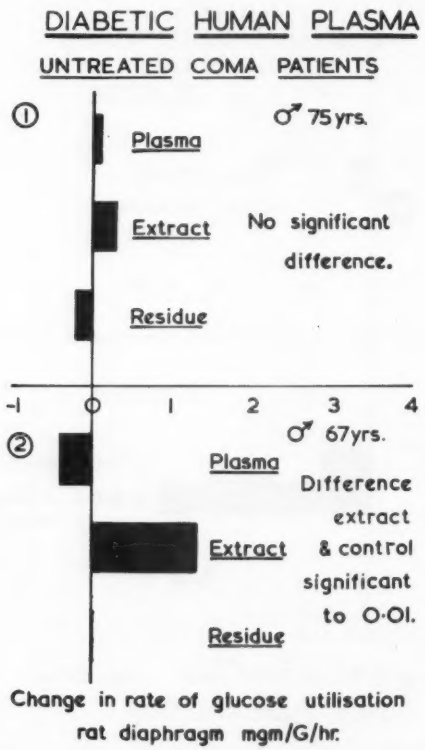

FIG. 3. Insulin assays of plasma, extract and residue; E. B. T. 3 technic.

hospital taking 200 units per day. She continued this dose for the next 12 months and enjoyed moderately good health. Then she began to suffer hypoglycemic reactions, and her dose was gradually reduced to 30 units per day. The cycle of resistance lasted nearly four years. She is still in reasonably good health, and her diabetes is adequately controlled with a daily dose of 24 units.

In both these patients the estimation of circulating insulin was determined by the effect of crude plasma upon A.D.H.A. rats. Both patients developed resistance over a period of some weeks for no obvious clinical

reason. During the phase of resistance no circulating insulin could be demonstrated. In one case passive transfer of resistance to animals was possible. Gradually, over some months, their insulin tolerance returned, and with this insulin was demonstrated in the blood stream.

More recently the detection of insulin has been attempted by a different technic. Estimations of the glucose uptake of the rat diaphragm have been made following the addition of crude plasma, of plasma extracts designed to concentrate the insulin content, and of the residue remaining after concentration.* These extracts are designed to remove lipids and lipoproteins which have previously been shown to inhibit glucose uptake of the diaphragm. The accelerating material has not yet been proved to be insulin, but there is strong presumptive evidence to suggest this.

The two patients now to be described were admitted to hospital in ketotic coma.

Case 3. A woman of 75 years gave a suggestive history of diabetes mellitus of one month's duration. She had received no treatment prior to admission to hospital in ketotic coma. No insulin was demonstrable in serum or in serum extract. Despite appropriate treatment, she failed to exhibit any response and died 16 hours after admission.

Case 4. A female of 67 years, a chronic alcoholic, had been known to suffer from diabetes for four years prior to admission. She was admitted to hospital in ketotic coma following neglect of treatment for some time previously. No insulin activity was demonstrable in her crude plasma, but an appreciable amount was present in the plasma extract. She died despite appropriate treatment.

It is tempting to speculate that the findings in these four cases were related in some way to a greatly increased demand for or increased destruction of insulin. In the words of Gowland Hopkins, "The normal progress of events in every living system calls for the presence of a number of highly specific substances, each exerting its own particular influence in a quantity which is almost infinitesimal; implying that the chemical equilibrium on which life depends may be balanced as it were on pin points." [9]

A different pattern of resistance was shown in two ketotic patients who had adequate amounts of insulin in their circulating blood but showed little therapeutic response to large doses of insulin.

Case 5. A female of 64 years was admitted to Alfred Hospital in severe ketosis on May 5, 1954. Diabetes had been diagnosed five years previously, and she had been treated with insulin since then. For several days prior to her admission she had apparently taken less than her usual dosage, as she felt unwell. Her normal dose was 56 units. She responded to treatment, and 1,350 units of insulin were given in the first 16 hours. Over the next few days it was apparent that she was in a state of resistance, and her insulin requirements varied from 200 to 400 units per day. During this time her general condition was not satisfactory. She complained of nausea and anorexia, and on the sixth day after admission she refused all food and lapsed into coma. Thirty-eight hundred units of insulin were given in the next 12 hours, with no demonstrable effect upon the level of her blood sugar, which remained at about

* Technic of E.B.T. 3 assay at end of manuscript.

1,000 mg./100 c.c. She died of circulatory failure. Autopsy revealed areas of acute pancreatitis, evident only on microscopic examination, and some atheroma of the left coronary artery and a mild renal arteriosclerosis. Ample insulin was demonstrated in the extract of her serum, but it seems that for some unknown reason she had lost the ability to use it.

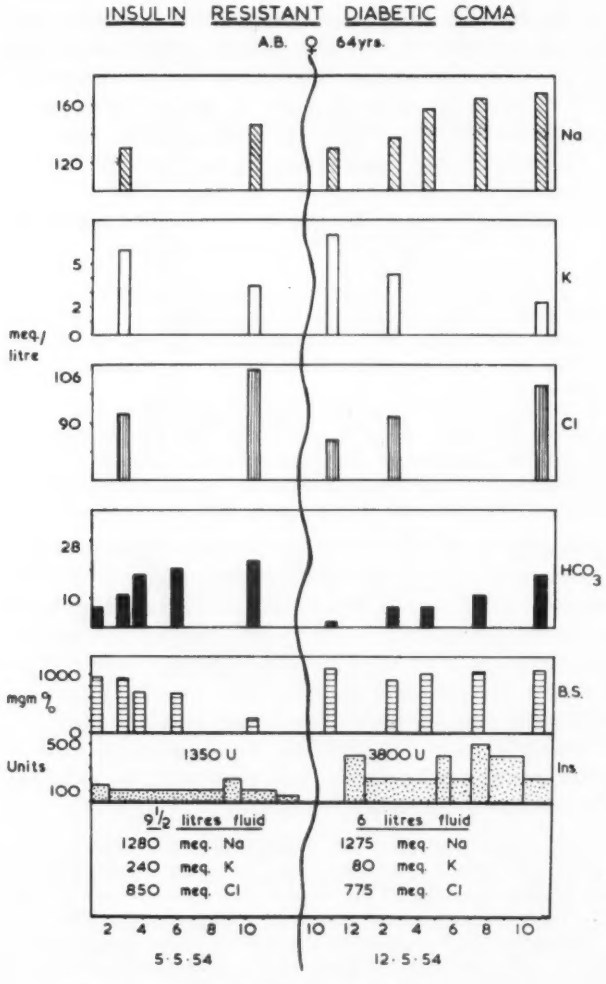

FIG. 4. Pattern of insulin resistance in case A. B.

Case 6. A female, aged 76 years, developed acute symptoms of diabetes in March, 1955. She was admitted to hospital and brought under control on an appropriate diet and a daily dosage of 120 units of Isophane insulin. For a few months her progress was satisfactory and then, because of persistent glycosuria, her dose was increased

to 156 units daily. In September, 1955, while awaiting re-admission to hospital for further study, she became thirsty and a few days later developed drowsiness associated with vomiting and was admitted to hospital as an emergency coma, with typical air hunger and dehydration. She was recognized as probably insulin-resistant on admission, and during the next 48 hours she received 11,400 units of insulin. During the

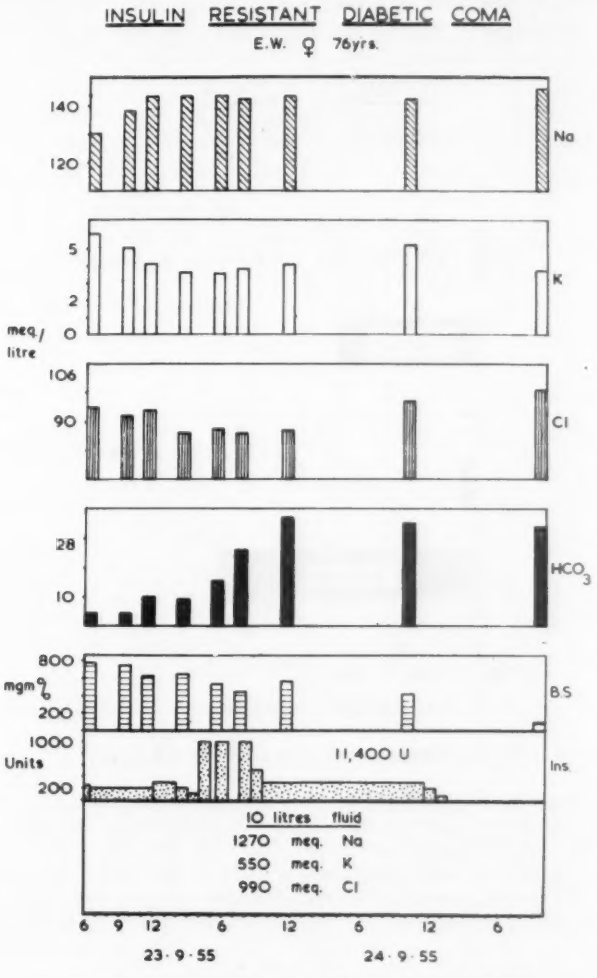

FIG. 5. Pattern of insulin resistance in case E. W.

first 30 hours this vast dose of insulin had little effect upon the level of blood sugar. Thereafter it seemed that her resistance was overcome and her clinical condition was much improved. However, she died suddenly for no obvious reason. Autopsy revealed a moderate degree of left ventricular hypertrophy, generalized atheroma and a

fatty liver. A sample of blood taken during the course of treatment, approximately 10 hours after the start of intensive insulin therapy, showed a large amount of insulin present in her extracted serum.

This patient exemplifies the well known clinical observation that on occasions it seems possible to overcome insulin resistance if sufficiently large doses are given, although with adequate amounts of insulin already in the blood stream it is difficult to understand why this is so.

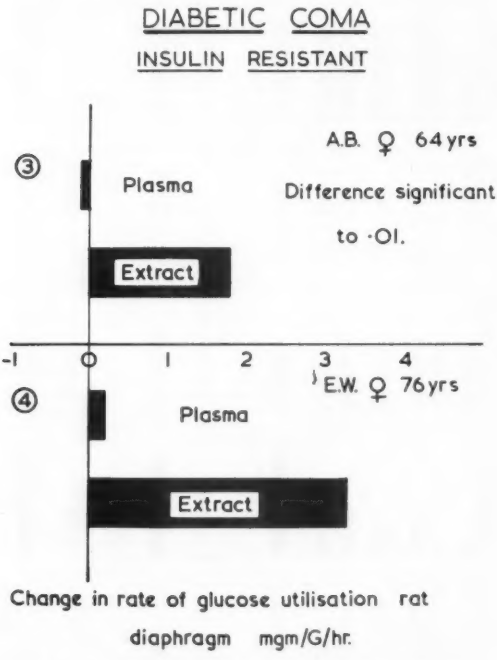

FIG. 6. Insulin assays in cases A. B. and E. W.

Case 7. Early in 1955 a male of 45 years developed typical symptoms of diabetes. He was admitted to hospital for the purpose of stabilization and was eventually controlled, with some difficulty, with a daily dose of 350 units. He has remained in an unsatisfactory state ever since, being subject to alternating hypoglycemia and ketonemia. His insulin dose has fluctuated within comparatively narrow limits, and ample insulin is demonstrable in his unextracted serum as well as in serum extracts.

From our experience, it would seem that insulin resistance does not always develop in the same way. While delay in absorption,[10] insulin antagonism, or over-action of physiologic opponents might possibly account for resistance in cases who have no demonstrable insulin in the blood stream, it is difficult to see how such theories are applicable to patients with adequate

insulin in their blood which is ineffective, or which the patient is incapable of using. One is reminded of a recent statement by J. B. S. Haldane: "The most typical biochemical abnormalities, as Garrod recognized 50 years ago, are metabolic blocks. They are due, at least in some cases, to the absence of the enzyme catalyzing a particular process." [11]

For the obvious reason of the time which is necessary to analyze serum, it is impossible for the physician to know whether he is dealing with true resistance during the critical hours of treatment of ketosis and, if so, whether it is associated with the presence or absence of circulating insulin. Indeed, if such knowledge were available at the bedside it would profit him little, for at present we are ignorant of any agent which facilitates insulin action. Nevertheless, in some instances resistance is a temporary state and if con-

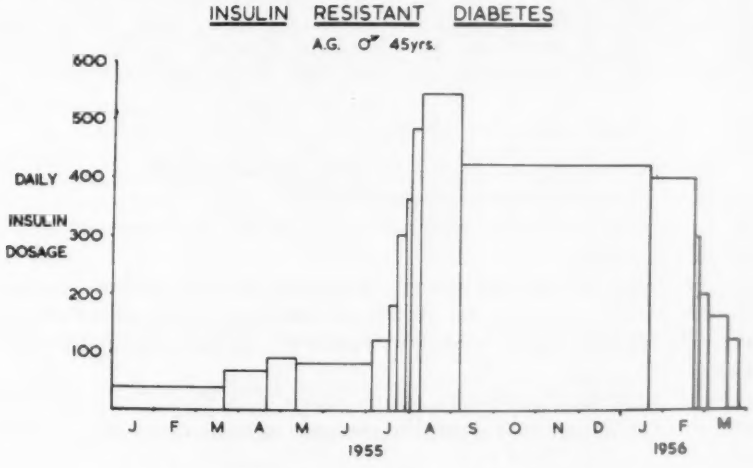

FIG 7. Pattern of insulin resistance in case A. G.

trolled, even inadequately, return to a conventional response to insulin can be anticipated.

It would be sheer presumption for me to attempt any discussion on theories of insulin action,[12] to become involved in arguments on transformation and translocation, or to propound theories of insulin resistance. A clear definition of a problem is necessary before any solution can be sought. Herein lies a fertile field for further study and for clinical research in its widest sense.

Case records have been presented to show the transient nature of this condition, with absence and subsequent return of insulin to the blood; to show that resistance in ketotic states can develop in the presence and absence of circulating insulin, and that continuing insulin resistance can occur in the presence of adequate blood insulin levels.

In these days of ever-increasing specialization and differentiation of knowledge, it is necessary for us constantly to remember that the clinician and the scientist each have a part to play. Clinical research and scientific research must proceed with due regard to their place in solving the problems of disease. Each must contribute to this relentless search, as Claude Bernard [18] emphasized 100 years ago, and his words have great application to the present day.

"I tell those whose path leads them toward theory or toward pure science, never to lose sight of the medical problem, which is to preserve health and cure disease. I tell those whose career, on the contrary, guides them toward practice never to forget that if theory is meant to enlighten practice, practice in turn should be of use to science. Physicians thoroughly imbued with these ideas will always keep their interest in the progress of science, at the same time that they do their duty as practitioners. In noting accurately and acutely the interesting cases that present themselves, they will understand how fully science may profit by them. Experimental scientific medicine will thus become the achievement of us all; and every one of us, even if he be only a simple country doctor, will make his own useful contribution."

Summary

1. For the satisfactory solution of many clinical problems, a combined approach by physician and scientist is desirable.

2. Certain aspects of the phenomenon of insulin resistance are used to illustrate this point.

3. Insulin resistance is at times a transient state, and in some instances, at the height of resistance, no insulin is demonstrable in blood plasma. Later, with the recovery of tolerance, insulin can be demonstrated in blood plasma.

4. Case records of patients in severe ketosis show that insulin resistance may develop at this time in either the presence or the absence of circulating insulin.

5. A case is cited where a persisting insulin resistance existed in conjunction with ample circulating insulin.

6. From this experience it can be assumed that insulin resistance does not necessarily arise in the same way in every instance.

Acknowledgments

I desire to express my thanks to Dr. J. Bornstein, who undertook all the estimations of blood insulin; to Dr. Bryan Hudson, who undertook the management of several patients in this series, and to Dr. Kathleen Taylor for the illustrations accompanying this lecture.

Technic of Extraction E.B.T. 3

One volume of heparinized plasma is extracted with a mixture of 4 vol. ethanol, 0.4 vol. butanol, 0.4 vol. toluene and sufficient hydrochloric acid to bring pH of the mixture to 3 (glass electrode).

After it has been stirred for one hour, the supernatant is removed and the precipitate is reëxtracted four times with a mixture of 1 vol. Na Ac 0.02M, 4 vol. ethanol, 0.4 vol. butanol, 0.4 vol. toluene. (The solvents must be carefully purified.)

The supernatants are combined and the total proteins are precipitated by an excess of acetone. The precipitate is recovered by centrifugation, partially air dried and then dried totally in a vacuum desiccator. The dry precipitate is suspended in saline at pH 3 and stirred. The insoluble portion is discarded and the soluble portion is neutralized and added to the test system.

With the use of $S^{35}04$ labelled insulin, the recovery is about 85%.

Summario in Interlingua

Le solution de multe problemas clinic require le cooperation de medico e scientista. Es presentate un breve description del phenomeno de resistentia a insulina. Le theorias de su origine es enumerate. Il es a notar que resistentia a insulina pote esser temporari. Il occurre casos de retorno al previe requirimentos de dosage.

Es presentate historias de casos de patientes qui habeva durante lor periodo de resistentia a insulina nulle demonstrabile concentrationes de insulina in lor plasma sanguinee. Post retorno del toleration de insulina, le plasma permitteva de novo le constatation de insulina. Altere protocollos—concernente patientes in statos de cetosis sever—indica que le resistentia a insulina pote disveloppar se rapidemente. In un tal caso nulle insulina in circulation poteva esser demonstrate. In un altere, adequate concentrationes de insulina esseva presente in le plasma. Es etiam citate un caso in que prolongate resistentia a insulina se disveloppava durante que le plasma sanguinee contineva adequate concentrationes de insulina.

Iste observationes permitte le conclusion que resistentia a insulina non se disveloppa in omne casos in le mesme maniera. Es exprimite le opinion que resistentia a insulina se presenta in iste lumine como un problema que va esser solvite le plus probabilemente per un attacco combinate ab le punctos de vista clinic e scientific.

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CASE REPORTS

AMINO-ACIDURIA WITH CYSTINOSIS: CASE REPORT WITH DETERMINATION OF URINARY AMINO ACIDS AND OCULAR CYSTINE *

By PHILIP L. DERN,† M.D., *San Francisco, California*

IN 1936 Fanconi described a syndrome including rickets, nephrosis, glycosuria and hypophosphatemia.[1] His suspicion that the organic acids excreted in large amounts were amino acids was partially confirmed by McCune in 1943.[2] The later history of the disease parallels the development of more exact means of determining amino acids. Dent found that patients with the Fanconi syndrome excreted many different amino acids in the urine, yet blood levels of amino acids were normal.[3] He distinguished two general types of amino-aciduria: those associated with marked amino-acidemia, as in severe liver failure, and those in which blood levels were normal but a renal tubular reabsorptive defect allowed excessive urinary excretion of the compounds.[4] The Fanconi syndrome is an example of the latter mechanism. This syndrome has most frequently been described in children,[2, 5] but adult cases have also been described.[23] Polyuria, failure of growth, rickets (osteomalacia in adults), episodes of dehydration, hypokalemia, hypophosphatemia with or without acidosis, renal glycosuria, and a generalized amino-aciduria are characteristic. The presence of Milkman's pseudofractures on the bone films of an adult with obscure bone pain may suggest the presence of this syndrome.[23]

Recently the author had the opportunity to study a case in a child in whom disease of the pituitary had been suspected.

CASE REPORT

A two and one-half year old male was first seen on February 1, 1954. His mother had noted that his growth had been poor for one year and that he awoke innumerable times during the night to urinate and to drink water. He was born of a normal, full term pregnancy. His birth weight was six pounds. Development of motor and mental functions followed a normal pattern. He had always received vitamin supplements containing vitamin D. There had been no previous major illnesses. Physical examination revealed a small, active child. Temperature was 37° C.; pulse, 120; systolic blood pressure, 110. Head circumference was 48.5 cm.; body length, 86.0 cm.; weight, 11.3 Kg., which placed him below the lowest percentile for height and weight on a standard growth chart. No frontal bossing of the skull was noted. No abnormalities of the eyes, ears, nose or throat were noted. The

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heart was not enlarged, and no murmurs were audible. The basal second sound was loudest at the pulmonic area. The liver edge was felt 6 cm. below the right costal margin. No masses were felt in the flanks. No abnormalities of the extremities were found, and the neurologic examination was grossly normal.

Laboratory work on entry showed a hemoglobin of 12.5 gm.%; hematocrit, 38; white cell count, 11,500, with a normal differential. The urine specific gravity was 1.003; protein and sugar were absent. The urine sediment was normal. The blood urea was 64.0 mg.%; serum carbon dioxide combining power, 19.1 mM/L.; serum chloride, 118.8 mEq./L.; serum potassium, 3.9 mEq./L.

Hospital Course: On February 4, 1954, 1 unit of Pitressin was given subcutaneously. Despite this, the urine specific gravity continued to be 1.002 to 1.004. On February 7, 1954, water was withheld from the patient, which resulted in a maximal urine specific gravity of 1.009, although a rise in hematocrit of from 38 to 42 occurred during the test. The two-hour phenolsulfonphthalein excretion was less than 15%. On February 8, 1954, the urea clearance was 33 c.c./min./1.73 m^2 surface area. Daily urine volumes ranged between 2,000 and 4,445 c.c., and at no time did the specific gravity exceed 1.004. The 24 hour urinary excretion of protein was 0.4 and 1.0 gm. Sulkowitch's test for urine calcium was repeatedly negative, and the 24 hour urinary calcium excretion was 81 mg. The 24 hour glucose excretion was 600 mg. Urine pH (nitrazine paper) remained near 6.5. Repeated examinations of the urine sediment failed to reveal abnormalities. The blood urea remained between 59 and 64 mg.%, and the serum carbon dioxide combining power stayed at about 19 mM./L. The initially high serum chloride (118.8 mEq./L.) fell to 99.7 mEq./L. during therapy. Hypokalemia and hyponatremia were not observed. Initially the serum phosphorus was 2.5 mg.%, later rising to 3.5 mg.%. Serum calcium was 10 mg.%, later 11.4 mg.%. The alkaline phosphatase was 12.1 Bodansky units initially, and 8.7 units later.

On February 6, 1954, intravenous pyelography failed to visualize the kidneys. No renal calcinosis was seen. On February 15, 1954, retrograde pyelograms revealed radiologically normal kidney structure and size. Bone survey showed a normal skull and sella. The epiphyseal cartilages of both hips, fibulas, tibias and femurs were widened, suggesting rickets. Three months later only slight irregularity of the epiphyseal lines remained. Bone age was two years (Greulich-Pyle standards). On February 12, 1954, examination of the bone marrow revealed no crystals. On February 18, 1954, the patient was examined under the slit lamp and numerous fine, superficial crystalline deposits were seen in the eyes (conjunctiva and cornea). A biopsy of the bulbar conjunctiva was obtained and numerous elongated crystals were seen on microscopy.

An aliquot of a 24 hour urine was obtained on February 17, 1954, and analysis showed an elevated amino-nitrogen content (163 mg. of amino-nitrogen per 24 hours;

TABLE 1

Urinary Amino Acid Excretion in Milligrams per 24 Hours

Amino Acid	Patient	Normal Three Year Old Child
Cysteine/cystine	97.2	10.0
Arginine	15.6	3.0
Threonine	96.0	1.6
Glycine	114.0	41.0
Histidine	27.0	40.0
Isoleucine	12.0	1.7
Lysine	58.0	2.0
Methionine	3.3	0.3
Phenylalanine	15.0	3.0
Tryptophan	24.0	6.0

normal is 1.0 mg. per pound of body weight or in this patient approximately 22.8 mg.). The blood amino-nitrogen was normal (5.4 mg.%). Microbiologic determination of certain urine amino acids revealed that their excretion was abnormally high and that a generalized amino-aciduria was probably present (table 1).

Determination of blood cystine, arginine and threonine revealed normal levels (2.4 mg.%, 1.8 mg.% and 1.8 mg.%). In a search for a possible familial renal tubular defect, the mother's urine was analyzed for cystine, arginine and threonine, and normal 24 hour excretion values were found. Analysis of the piece of conjunctiva obtained by biopsy was done, utilizing two-dimension paper chromatography.*

Results of the analysis of the tissue biopsy showed that large quantities of cystine were present, establishing the presence of cystinosis in addition to the Fanconi syndrome.

The patient remained very active throughout his hospital stay. He was discharged on milk, vitamin D and a mixture of sodium citrate and citric acid. Six months later his weight had decreased one and one-half pounds, and his height had not increased. Except for two episodes of respiratory tract infection and occasional episodes of abdominal pain, he has had no other difficulties.

Discussion

The Fanconi syndrome is related to a number of renal tubular defects which have a hereditary tendency.[6] Renal glycosuria is perhaps the simplest example of such a defect. A more extensive defect is present in Wilson's disease, in which amino acids and glucose fail to be reabsorbed normally from the glomerular filtrate.[7] Certain cases of "refractory rickets" and Milkman's syndrome may have faulty tubular reabsorption of phosphate as the primary difficulty. Finally, in the Fanconi syndrome, defects in the reabsorption of amino acids, glucose, electrolytes and water occur. The term "renal rickets" is often applied indiscriminately to any case of rickets or osteomalacia occurring with renal disease. The inadequacy of this term is well illustrated by the Fanconi syndrome. Rickets or osteomalacia may occur when too little serum phosphate is present for the level of serum calcium, or if the level of serum calcium is primarily inadequate.[8] The differences in the mechanisms for bone disease in glomerular and tubular insufficiency have been emphasized.[6, 8] Early in the Fanconi syndrome the defect is predominantly tubular, and the bone disease is probably due to hypophosphatemia secondary to impaired tubular reabsorption of phosphate from the glomerular filtrate.[9] Later in the disease, as azotemia and glomerular insufficiency develop, the serum phosphate rises and a second mechanism for development of bone disease occurs.

The urine of normal individuals contains small amounts of amino acids which escape tubular reabsorption. Amino-aciduria of abnormal degree occurs in severe liver disease and may be due to "overflow" secondary to high blood levels.[4] A renal basis for the amino-aciduria seems probable in the Fanconi syndrome and Wilson's disease,[7] and for the various toxic tubular nephropathies such as that due to uranium poisoning.[20] In a few situations specific amino acids seem to be excreted to a predominant extent. In pernicious anemia with neurologic disease, large amounts of taurine were reported to be excreted.[21]

* The dinitrophenyl derivatives of the tissue amino acids were made by reacting the tissue extract with dinitrofluorobenzene. The resulting dinitrophenyl amino acids were separated from the proteins by ether extraction. Two dimension paper chromatography demonstrated large amounts of dinitrophenyl cystine and only trace amounts of other amino acids.

Large amounts of beta-amino-isobutyric acid were excreted in a case of lead poisoning.[30] Amino-aciduria also occurs in burns,[22] galactosemia,[31] after adrenal steroid administration,[32] and in muscular dystrophy [33] and pregnancy.[34] Hyperamino-aciduria was not found in a variety of cases of renal disease of the usual types in which some other manifestations of tubular insufficiency were present.[41]

Cystinuria is a disease to be distinguished from the Fanconi syndrome. This is a limited amino-aciduria associated with renal tubular defects in the handling of cystine, arginine, lysine and ornithine, whereas excessive amounts of many different amino acids are excreted in the Fanconi syndrome. Cystinuria is compatible with good health, but a tendency exists for the formation of renal calculi composed of cystine. A survey of a large number of presumably healthy individuals has demonstrated the presence of cystinuria in a few.[10] Cystine, arginine and lysine have similar structural formulas and may be handled by the same renal tubular transport mechanism.[11]

Certain cases of the Fanconi syndrome in children may be associated with increased tissue deposits of cystine. These cases of cystinosis may have normal blood levels of cystine, as in our patient, or the levels may be elevated.[12] In the cases with normal blood levels one must assume that a local tissue metabolic defect leads to deposition of the cystine,[13] or that acute episodes of hyperaminoacidemia develop, perhaps secondary to dehydration.[14] It is of interest that cystinosis has never been reported in an adult case of the Fanconi syndrome. Glycosuria may be present early in the Fanconi syndrome,[3] but apparently may be absent in the later stages of the disease, as in our case. As glomerular insufficiency becomes superimposed on the tubular lesion, tetany due to hypocalcemia occurs.[2] During the phase of tubular insufficiency, episodes of hypokalemia occur.[2, 12] In the cases with cystinosis, cystine crystals are often demonstrable in the bone marrow and in the corneal and conjunctival tissue, as well as elsewhere, especially in the tissue of the reticuloendothelial system.[16, 35, 36, 37, 38, 39] Most of the cases have been described in children, and death occurs early due to uremia or infection. Striking improvement has been reported after the use of large doses of vitamin D and electrolyte-containing supplements.[12]

In the Fanconi syndrome the site of the difficulty seems to be the proximal convoluted tubule. Both phosphate and glucose are absorbed from the glomerular filtrate in this region.[17] In cystinosis, when this has become superimposed upon the Fanconi syndrome, severe pathologic changes have been found in the cells of this portion of the renal tubule. These changes resemble those occurring in experimental uranium poisoning,[14] and the occurrence of aminoaciduria in uranium toxicity is known.[18] However, cystine itself may be nephrotoxic.[14] The absence of phosphatase in the cells of the renal tubule, in which it normally occurs, has been described in the Fanconi syndrome.[18] Recent cytochemical work further delineates the locus of amino acid transport in the kidney. Parenteral injection of amino acids in the rat resulted in the formation of mitochondria-amino acid complexes within the cells of the proximal tubule. It has been suggested that these complexes are the sites of amino acid concentration, metabolism and transfer.[25] In the dog, at least three separate transport systems exist for the tubular reabsorption of amino acids. One system seems to handle glycine; another handles leucine and isoleucine; and a third handles arginine,

histidine and lysine.[24] Although Dent found a parallel relationship between the excretion of amino acids and the excretion of glucose,[18] this need not occur, as in our case. Different mechanisms for the reabsorption of glucose and amino acids have been found.[40] Alanine and glycine may share a common tubular transfer mechanism with phosphate.[20]

In contrast to the Fanconi syndrome, in which proximal tubular function seems most impaired, a group of diseases exists in which the emphasis is upon distal tubular dysfunction and inability to excrete an acid urine.[6] In the Butler-Albright syndrome, rickets, acidosis, diabetes insipidus and nephrocalcinosis occur.[26] The phosphaturia and the calcinuria appear to be secondary to the acidosis. Renal calcinosis is not a feature of the Fanconi syndrome, in which urine acidification may be relatively normal. In the Fanconi syndrome the bone disease is largely due to the phosphaturia, and hypercalcemia with renal calcinosis is therefore infrequent.[23] A syndrome allied to the Butler-Albright syndrome has been described by Lightwood.[27] In this condition, hyperchloremic acidosis and renal calcinosis occur during the first 18 months of life but are reversible with age. Presumably, immaturity of the renal tubules is the basis for the temporary dysfunction.[27, 28]

Summary

1. A case of the Fanconi syndrome with cystinosis is presented. Isolation of cystine directly from ocular tissue was done. Microbiologic analysis of the urine indicated the presence of a generalized amino-aciduria.

2. A general review of the mechanisms of bone disease and amino-aciduria is made, and the Fanconi syndrome is distinguished from cystinuria and from the Butler-Albright and Lightwood syndromes.

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Summario in Interlingua

Le autor describe un caso del syndrome de Fanconi con cystinosis occurrente in un puero de duo annos e medie de etate. Le patiente habeva un historia de un anno de polyuria e manco de disveloppamento. Basse gravitates specific del urina que non esseva alterate per le administration de Pitressina suggereva le presentia de un lesion renal. Esseva constatate un reducite clearance de urea e un reducite excretion de phenolsulfonphthaleina. Acidosis hyperchloremic e hypophosphatemic esseva presente. Le roentgenogrammas del ossos demonstrava rachitis. Specimens bioptic del conjunctiva esseva analysate per chromatographia a papiro. Isto revelava que le fin depositos crystallin vidite in le examine del cornea e del conjunctiva per medio del lampa a fissura consisteva de cystina. Le analyse microbiologic del amino-acidos urinari revelava augmentate nivellos del excretion de omne le 10 amino-acidos testate.

Le nivellos sanguinee de amino-nitrogeno esseva normal. Es presentate un revista del litteratura del thema. Le syndrome de Fanconi es discutite in relation a altere morbos del proximal tubulo renal.

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GOITERS IN TWINS RESULTING FROM PROPYLTHIOURACIL GIVEN DURING PREGNANCY *

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These cases warrant comment since no report has appeared in which twins were born with goiters iatrogenically produced with propylthiouracil and iodine. No clinical evidence of hypothyroidism appeared in the infants.

Case Report

A three months pregnant, 41 year old white female had complained of increasing nervousness, severe palpitation, easier fatigue, weakness and increased sweating for several months. There was no history of diarrhea, heat intolerance, insomnia or previous symptoms to suggest thyroid dysfunction. Examination revealed an apprehensive patient with a resting pulse rate of 138 beats per minute. After one hour's rest the pulse rate was 120. A mild tremor of the fingers was noted. Blood pressure was 168/80 mm. of Hg. A nodule was palpable in the left lobe of the thyroid gland. No eye signs or bruits were present. A grade 1 systolic murmur was audible. A basal metabolic rate was plus 36. Propylthiouracil, 100 mg. every eight hours, Lugol's solution, drops 5 three times a day after meals, vitamins and a high caloric diet were prescribed and taken through the prenatal period. The patient improved, and all symptoms due to the hyperthyroid state disappeared six to eight weeks after therapy had been started.

One week past the expected date of confinement twin girls were born. The twins were believed to be fraternal because of separate amnions, chorions and marginally joined placentas. The first baby, M. F. N., weighed 5 pounds 5 ounces. Measurements were as follows: head, 12¾ inches; chest, 11½ inches; length, 19 inches. Following cephalic presentation the infant breathed spontaneously and exhibited good color. She appeared to be a mature baby, although the birth weight was in the premature range. Abnormal physical findings were limited to an irregular, dumb-bell shaped, fairly soft mass, approximately 7 by 3 by 2 cm., in the anterior portion of the neck. The goiter was not nodular, warm or tender.

The other baby, A. M. N., delivered five minutes later by breech presentation. This infant weighed 6 pounds 5 ounces. Measurements were as follows: head, 13½ inches; chest, 12 inches; length, 19½ inches. The infant breathed spontaneously. A mass similar to the one in the other twin was seen in the anterior portion of the neck. The ease with which tubes were passed in each twin confirmed the patency of each esophagus.

Aspiration of an evaporated milk formula by A. M. N. occurred on the eighth day, resulting in mild cyanosis. Uneventful recovery followed cleansing of the airway and the use of oxygen. Penicillin and streptomycin were used prophylactically.

Monthly evaluations have shown alert, active girls without evidences of hypothyroidism. The twins have progressed as rapidly as any of the other five siblings. Throughout the first year of life the twins have appeared to be non-identical. They have consistently shown normal physical examinations, including ophthalmoscopic

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and neurologic evaluation. At five months they sat alone, and at six months both crawled. At nine months both of the infants could pull to a standing position. Weights at nine months of age were 15 pounds 10 ounces for A. M. N., and 18 pounds 8 ounces for M. F. N. Both goiters were small by the age of three months and had completely disappeared by the age of nine months.

FIG. 1. Photographs of twins at five days of age showing iatrogenic goiters.

COMMENT

Relatively little has been written concerning the use of propylthiouracil during pregnancy and of its effect on the fetus.[1-8] Hepner [4] reviewed the literature and found reports of 30 infants born of hyperthyroid mothers who had

been treated with thiourea derivatives during pregnancy. Two of these infants had transient enlargement of the thyroid gland. In the group of mothers treated with the thiourea derivatives, no goitrous infant was born of any mother who had in addition received iodine during pregnancy. Hepner therefore recommended iodine administration, feeling that it might inhibit formation of thyrotropic hormone in the fetus. It is significant to note, however, that our patient had iodine from the third month of pregnancy through term and yet both infants had goiters. Although cretinism has been reported from antithyroid drugs given during pregnancy, there has been no evidence of hypothyroidism in the twins reported in this presentation.

Summary

1. This is the first report of goiters in twins produced by propylthiouracil administration during pregnancy.

2. The goiters were transient, and were not associated with clinical evidence of thyroid dysfunction.

3. Iodine in conventional dosage as given to the mother apparently did not inhibit the formation of thyrotropic hormone in the fetus.

4. Propylthiouracil and iodine are not contraindicated during pregnancy if hyperthyroidism is present in the mother.

Summario in Interlingua

Le casos hic reportate merita commento proque il existe in le litteratura nulle altere reporto de geminos nascite con struma de production iatrogenic per le administration de propylthiouracil e iodo al matre. Nulle signo clinic de hypothyroidismo esseva notate in le infantes.

Un 41-enne femina blanc, gravida le tertie mense, habeva symptomas e signos que indicava hyperthyroidismo. Le pulso in stato de reposo esseva 120; le pression sanguinee, 168/80 mm Hg; le metabolismo basal, + 36. Le symptomas del hyperthyroidismo dispareva intra octo septimanas post le initiation del tractamento con propylthiouracil (100 mg omne octo horas), solution de Lugol (5 guttas post repastos tres vices per die), vitaminas, e dieta a alte valor caloric.

Pueras gemine, nascite un septimana post termino, pesava 2410 e 2860 g. Illas esseva considerate como geminas fraterne. Le examine physic revelava nulle anormalitate, excepte le strumas que mesurava in ambe geminas circa 7 per 3 per 2 cm.

Evalutationes mensual ha monstrate que le geminas es alerte e active pueras qui exhibi nulle signo de hypothyroidismo. Illas progredeva tanto rapidemente como lor cinque fratres e sorores. Illas sedeva sin supporto a cinque menses, reptava a sex menses, e traheva se in position erecte a nove menses.

Al etate de nove menses le peso del primogenita esseva 8,390 kg. illo del secunda 7,090 kg. Ambe strumas esseva parve al etate de tres menses e habeva disparite completemente al etate de nove menses.

Hepner trovava in le litteratura reportos de 30 infantes nascite ab matres hyperthyroide qui habeva essite tractate durante lor pregnantia con derivatos de thiourea. Duo de ist infantes habeva transiente allargamentos thyroide, sed in iste serie nulle infante con struma esseva parturite per un matre qui habeva recipite durante su pregnantia iodo insimul con un derivato de thiourea.

Ben que cretinismo ha essite reportate como effecto de drogas antithyroide administrate al matre durante su pregnantia, nulle signo de hypothyroidismo esseva notate in le casos del presente reporto. Isto es le prime reporto de struma in geminas, producite per le administration de propylthiouracil e iodo durante le pregnantia.

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ABDOMINAL "ANGINA": THE SYNDROME OF INTERMITTENT ISCHEMIA OF MESENTERIC ARTERIES*

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THE clinical and physiologic problems of vascular spasm and intermittent ischemia have been dealt with critically by Pickering.[1] Spasm of sclerotic vessels seems an unlikely cause of symptoms which occur with such irregular periodicity that spasm is a clinically appealing explanation. We have come to recognize syndromes associated with impaired circulation in coronary, cerebral and mesenteric arteries, and the larger arteries to the limbs. Thromboses of major arteries, when they occur suddenly and involve a vital or accessible structure whose function is impaired, are recognized quickly. Spasmodic or organic obstruction of vessels is suggested by the clinical features of the Raynaud complex, though the degree or, indeed, the very existence of spasm as a mechanism has been difficult to establish. Typical examples of intermittent ischemia with pain from impaired blood flow to the lower extremities, angina pectoris in which ischemia of the heart muscle gives rise to paroxysmal symptoms, and the clinical state of intermittent paralysis or paresis induced by partial or total occlusion of the carotid artery are situations we recognize without much difficulty. Obstruction of the capillary bed is recognized with greater difficulty. Such obstruction may cause fibrotic or occlusive vascular disease of the lung which ultimately, by a throttling mechanism, may extinguish the life of the victim. The problem of venous obstruction is exemplified by phlebothrombosis, thrombophlebitis, and the risk of pulmonary embolism.

Among the clinical disorders which give rise to signs and symptoms with a pattern consistent enough to be recognized has been the illness produced by arteriosclerosis of mesenteric vessels. The pain tends to be provoked by eating, and is therefore intermittent or paroxysmal. It has been given the name "abdominal angina." Whereas the term "angina pectoris," a choking or strangling, a quinsy of the chest, though inept, is thoroughly established in the minds of physicians and patients alike, the term "abdominal angina," suggesting a choking or strangling of the bowels, might have one implication for the physician, another for the surgeon, and yet another for the patient. Also, the possibility of confusing the term abdominal angina with the symptoms produced when angina pectoris gives rise to pains felt in or referred to the abdomen is another reason

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why the term is undesirable. For this reason, the term "intermittent mesenteric ischemia" is preferable.

The clinical features of mesenteric thrombosis in its classic form are well recognized and ordinarily provoke no great diagnostic confusion. On the other hand, the symptoms produced by intermittent mesenteric ischemia are less well known. They deserve emphasis, particularly since arteriosclerosis has become such a major problem in our aging and sclerotic society.

We have yet another reason for discussing the particular patient under consideration. This is our misinterpretation of the significance of the dramatic relief of abdominal pain he had when leaning forward in the sitting position. Such relief of pain we had observed hitherto only in patients with carcinoma, particularly of the body and tail of the pancreas, or other eroding retroperitoneal neoplasms or lymphomas. The relief of such pain was assumed to result from the gravitational shift which reduced tension or pressure on the sensitive structures of the celiac and splanchnic plexuses usually incorporated in or invaded by the tumor. In fact, this clinical characteristic of relief of abdominal pain in the prone, the right or left lateral position, or in the sitting position bent forward over the back of a chair or bed, we had come to accept as very strong evidence for the presence of a retroperitoneal tumor. This same phenomenon was a striking feature of the patient under consideration, but the mechanism was entirely different.

Case Report

A 41 year old white laborer was admitted to the medical service of the University Hospitals on January 8, 1956, complaining that he had begun to have severe attacks of epigastric pain seven months before admission. He had been in excellent health until the abdominal pain began. The pain was not associated with chills, fever, jaundice, nausea, vomiting or diarrhea. It followed no trauma. At the onset, the pain was brought on by eating greasy food. It commenced a few minutes to an hour after eating. It occurred about once a week and lasted six to eight hours. It was constant, not colicky. Later the pain became continual. Eating any type of food made it worse. It got more severe and radiated through to the back. Pain was relieved by injections of narcotics. He could get some ease in the sitting position, especially when leaning forward. He reported black, tarry stools two months prior to admission. He had lost 110 pounds in the previous six months. He had been studied several times by physicians. X-rays of the alimentary canal were normal. He was told that he had a nervous stomach. He denied the use of alcohol. He had had no abdominal operations. The past history, family history and social history contributed no clue.

On entrance physical examination he was a chronically ill white man with evidence of great weight loss. He complained of severe abdominal pain. His blood pressure was 140/100 mm. of Hg; pulse, 72 and regular. The heart was not enlarged and was not overactive; the rhythm was regular. The epigastrium was tender on palpation. The sharp and non-tender liver edge could be felt on deep inspiration. No masses were felt. The rest of the examination was normal.

Laboratory tests revealed a normal urine. Hemoglobin was 14.3 gm.; white blood cells, 9,400, with a normal differential count. The sedimentation rate was 25 mm./hr. (Westergren), and the hematocrit was 44%. The Kolmer and V.D.R.L. were negative. Examination of the stool for blood was positive. The electrocardiogram was normal. A glucose tolerance test was abnormal, with elevated blood sugar

levels of 142 mg.% at 90 minutes and of 152 mg.% at two hours. Liver function studies were within normal range.

X-ray examination showed pulmonary emphysema, a normally functioning gallbladder and a normal colon. X-ray of the upper alimentary canal showed a normal stomach, but there appeared to be an incomplete obstruction at the junction of the third and fourth parts of the duodenum.

Hospital Course: A clinical diagnosis of carcinoma of the body of the pancreas was made because of the peculiar position-relief of pain and the abnormal duodenal x-ray. The patient was transferred to the Surgical Service. He continued to complain of severe abdominal pain and required frequent injections of Demerol for relief. His appetite was good but he refused to eat because eating any kind of food increased the pain. Intravenous fluids were administered. A right splanchnic and left celiac sympathetic block was performed, with immediate relief of pain which lasted only four hours. An exploratory laparotomy through a transverse incision was done on January *27*, with completely negative findings, including an operative cholangiogram. The mesenteric arteries were not noted to be unusual. The intestines were normal. The wound was closed and the patient returned to the ward in good condition. The cause of the pain remained obscure. The first 36 hours after operation were uncomplicated. He then vomited about a quart of dark fluid which tested positive for blood. He was not in pain at this time. Six hours later he had a profuse sweat. Fifteen minutes later he was found pulseless on the floor. He died approximately 66 hours after the operation, *22* days after admission to the hospital.

At postmortem examination he was found to have a thrombosis of the superior mesenteric artery. It originated at the site of extreme narrowing of the lumen caused by an arteriosclerotic plaque. This resulted in infarction of the entire small bowel and two thirds of the colon. There were severe peritonitis and hemorrhagic bronchopneumonia of the dependent parts of the lungs. There was an extrinsic fibrous band at the junction of the second and third portions of the duodenum which had caused the deformity seen on x-ray.

Discussion

We have reported a patient who had intermittent mesenteric ischemia produced by an arteriosclerotic narrowing of the superior mesenteric artery, giving rise to symptoms during the phase of digestion when the blood supply of the small intestine could not be increased to provide the increased demands of digestion and assimilation. The connection of pain and eating was so clearly perceived by the patient that he had almost stopped eating. He died of mesenteric thrombosis after an operation in search of a retroperitoneal tumor which we had diagnosed confidently but altogether in error.

The problem of so-called abdominal angina has been emphasized by Dunphy,[2] McClenahan and Fisher,[3] Berman and Russo [4] and others. The occurrence of acute coronary occlusion which simulates acute abdominal disease with pain confined to the abdomen has been investigated in detail by Field, Pordy and Master [5] in a study in which close attention was paid to the problem of the abdominal site of origin and the distribution and radiation of pain in myocardial infarction. One of us (W.B.B.) called attention to the epigastric location of origin of pain in 29 out of 144 cases of acute myocardial infarction.[6]

It is known that intra-abdominal disorders giving rise to pain, particularly those involving the biliary system, may produce arrhythmias reflexly. Under circumstances not completely understood, characteristic anginal attacks may be

associated. Such attacks are sometimes—but not always—relieved by operative correction of the cholecystitis and cholelithiasis.

Angina pectoris was recognized as a clinical problem several medical generations before myocardial infarction came to be understood widely. For a long time cardiac infarction remained a curiosity of major interest to the pathologist. On the other hand, mesenteric thrombosis was clearly established as a clinical entity with reasonably predictable clinical signs and symptoms, but the less severe manifestations of abdominal vascular ischemia were recognized much later. In our patient, death occurred as a result of mesenteric thrombosis. It is possible that operative intervention hastened the occurrence of this complication. It might have occurred spontaneously. We wish to emphasize particularly that the relief of abdominal pain by lying face down or by leaning forward has more than one possible explanation. In this man the relief induced by change in position resulted from the improved circulation when tension and drag on the fanlike suspension of the bowel by the mesentery were released or lessened. Eating food increased the need for blood, and where this basal flow was already near maximal the demand could not be met. Thus digestion produced pain with exasperating regularity.

Summary and Conclusions

1. Abdominal pain produced by intermittent ischemia of the mesenteric arterial circulation should be suspected when patients present the following complaints:

A. Persistent and consistent abdominal pain occurring regularly 30 to 60 minutes after eating.

B. Relief or moderation of the pain by assuming a position which reduces the drag on the mesentery and thus relieves the added mechanical impediment to the blood flow.

2. Pain from intermittent mesenteric ischemia as well as from retroperitoneal tumors may be relieved by lying in a special position on the belly or side, or by leaning forward while sitting.

Summario in Interlingua

Le problema de spasmo vascular e ischemia intermittente es recognoscite depost multe annos. On lo ha describite como occurrente in multe differente systemas organic, como per exemplo le corde, le gambas, le vias de alimentation. Quando le vasos mesenteric es le sito del reducite fluxo de sanguine, il deveni multo plus difficile interpretar le symptomas.

Le termino "angina abdominal" deberea esser reimplaciate per le termino "intermittente ischemia mesenteric" quando il se tracta de dolores producite per un reduction del fluxo sanguinee a transverso le vasos mesenteric.

In le caso hic reportate, le patiente habeva un typic historia de carcinoma del pancreas. Su dolores occurreva post le repastos e esseva alleviate in position sedente e inclinate in avante. Le examine physic e studios laboratorial pareva confirmar iste impression. Esseva constatate forte grados de sensibilitate del epigastrio, un anormal curva de toleration de glucosa, e signos roentgenologic de un incomplete obstruction del tertie e quarte portiones del duodeno. Un laparotomia exploratori esseva interprendite e resultava in constatationes completemente negative. Etiam le cholangiogrammas obtenite durante le operation esseva negative.

Le patiente moriva subitemente 66 horas post le operation. Le examine post morte revelava un thrombosis del arteria supero-mesenteric al sito de su reduction. Le causa esseva un placa arteriosclerotic. Le effecto esseva un infarcimento del integre intestino tenue e de duo tertios del colon.

In nostre experientia passate, dolores occurrente regularmente 30 a 60 minutas post repastos e alleviate per un position sedente e inclinate in avante se revelava como causate per carcinoma specialmente del corpore e del caude del pancreas o per altere erosive neoplasmas o lymphomas retroperitoneal. Le alleviamento positional del dolores ha essite interpretate como effecto del reduction del pression super structuras sensibile, como per exemplo le major plexos abdominal in le systema autonome. Le caso hic reportate illustra que un simile alleviamento postural de dolores postprandial pote esser observate in intermittente ischemia mesenteric.

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AGRANULOCYTOSIS DUE TO PHENYLBUTAZONE*

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It is well known that phenylbutazone is a hazardous medication, although it has been very effective therapeutically in relief of pain of arthritis and similar conditions. Bruck et al.[1] studied the toxicity of phenylbutazone and reported the following as being the usual toxic effects: epigastric pain and burning, dry mouth, buccal irritation, edema, urticaria, diarrhea, headache, purpura, and precipitation of oliguria and renal failure. Their series did not include agranulocytosis or neutropenia, but this is a recognized danger.

Beutler and Bergenstal [2] reported a case of perforated duodenal ulcer with neutropenia. The bone marrow in this case showed maturation arrest at the myelocyte stage. Steel and Moffatt [3] reported a case of Stevens-Johnson syndrome and granulocytopenia. The bone marrow in this case also showed maturation arrest at the myelocyte stage. O'Brien and Storey [4] reported a case

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of death from hypersensitivity due to phenylbutazone. The chief autopsy findings were polyarteritis nodosa and hypersensitivity angiitis. Cone, Hannigan and Teicher [5] and Nassim and Pilkington [6] have reported hypersensitivity reactions also. Wood [7] reported a fatal case of agranulocytosis following this drug. Death was due to septicemia. Engleman and his coworkers [8] have recently emphasized the danger of hepatic damage by phenylbutazone.

This case is reported to emphasize the necessity of constant vigilance while phenylbutazone is being administered.

Case Report

The patient was a 51 year old white female admitted to Boulder-Colorado Sanitarium and Hospital September 14, 1954, with the chief complaint of a sore throat. She had had a herniated cervical disc for three months. Various treatments, including traction, Tolserol, diathermy, aspirin, Demerol and a supportive collar, had been tried without significant relief. On August 7, 1954, the patient was started on a course of 400 mg. phenylbutazone daily, with marked relief from pain. The initial hemogram showed mild hypochromia but no other abnormality. Subsequent hemograms at two week intervals were normal. Two days prior to admission she developed a diffuse macular rash, and 24 hours later a fever and sore throat. Physical examination on admission revealed an acutely ill white female. Blood pressure was 142/78 mm. Hg. The pulse rate was 88 per minute, and the oral temperature 100.8° Fahrenheit. The pharynx was reddened and partially coated by scattered exudate. The neck was tender over the fourth cervical vertebra. Heart, lungs and abdomen were apparently normal. Urinalysis on admission was normal. Serology was negative. Hematologic findings during the entire hospital stay are summarized in table 1.

Course: Patient was given penicillin and streptomycin. A diffuse drug rash appeared, and Cortone was given for the presumed penicillin sensitivity. The patient continued acutely ill and febrile until September 22, nine days after admission, when definite proof of granulopoiesis appeared. The leukocyte count then became elevated and the patient made a prompt recovery from the agranulocytosis and pharyngitis.

Discussion

It is of interest to note that administration of the phenylbutazone was stopped two days prior to admission. Thus it appears that it was 11 days after the drug was stopped before bone marrow function was restored. This supports the report of Bruck et al.,[1] who found that it was 10 to 21 days after medication was stopped before blood levels of phenylbutazone reached zero. It is of interest that in Wood's [7] case a skin rash appeared six days after medication was stopped, and that recovery of marrow function did not occur until 19 days after cessation of the drug.

It is also of interest to note that in a case reported by Jespersen [9] a thrombocytopenia appeared after only two weeks of medication. This case took five weeks to develop symptoms. Wood's [7] case developed symptoms after 27 days. The time interval is not constant. Therefore, frequent hemograms must be done, and the physician must be aware of the other possible toxic symptoms at all times during administration of phenylbutazone.

TABLE 1

Summary of Hematologic Findings

	September															October	
	15	16	17	18	19	20	*21	22	23	24	25	26	27	28	29	1	3
Hemoglobin, gm. %	12					10.5				12.2							15.9
Erythrocytes	3.74					3.35				3.84							4.85
Leukocytes (total)	750	900	1,850	1,500	1,750	1,600	2,600	4,300	6,400	11,400	14,900	12,000	17,600	20,300	14,600	10,650	8,850
Granulocytes, %	2						17	32	59	60	67	53	71	61	55	54	48
Segmented, %	2						13	16	26	28	32	30	45	44	47	49	45
Stab, %							4	12	17	18	25	21	17	16	8	5	3
Metamyelocytes, %								2	7	7	8	2	5	1			
Myelocytes, %								1	6	5	2		3				
Promyelocytes, %								1	3	2			1				
Lymphocytes, %	96	95	99	92	93	92	70	55	31	35	29	40	23	33	39	42	39
Monocytes, %	2	5	1	8	7	8	13	13	10	5	4	7	6	6	6	4	14

* Transfusion, afternoon of September 20: 500 c.c. whole blood.

Summary

A case of agranulocytosis due to phenylbutazone is reported. The need for constant awareness of the toxicity of this drug is emphasized.

Summario in Interlingua

Es presentate un breve revista del effectos toxic de phenylbutazon. Iste effectos include dolores epigastric e pyrosis, siccitate e irritation buccal, edema, urticaria, diarrhea, mal de capite, purpura, oliguria, e disfallimento renal. Lesiones hepatic, reactiones de hypersensibilitate, thrombocytopenia, e agranulocytosis pote occurrer.

Le caso presentate es illo de un femina blanc de 51 annos de etate qui disveloppava rash, febre, pharyngitis, e agranulocytosis post cinque septimanas de tractamento con phenylbutazon pro un herniate disco cervical. Le constatationes hematologic durante le tractamento hospitalari es summarisate.

Circa 11 dies post le discontinuation del droga, le patiente manifestava signos de restablite functiones medullari. Isto es de accordo con le reporto de Bruck e associatos qui trovava que le nivello sanguinee de phenylbutazon reattingeva un nivello de zero solmente inter le decime e le vinti-prime die post le discontinuation del droga.

Le tempore del declaration del symptomas varia ab un caso al altere. Per consequente un vigilantia constante es necessari. Frequente hemogrammas debe esser obtenite, e le medico debe esser conscie del altere possibile symptomas toxic durante omne le phases de un curso de phenylbutazon.

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PRIMARY SYSTEMIC AMYLOIDOSIS WITH CARDIAC INVOLVEMENT AND WITH RUSSELL BODIES IN BONE MARROW*

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This case report concerns a patient who presented a diagnostic problem of cardiomegaly and myocardial failure of unknown etiology and in whom the outstanding pathologic finding at autopsy was primary systemic amyloidosis with marked cardiac involvement. An additional finding of great interest was the presence of numerous Russell bodies in the bone marrow. For previously reported cases (approximately 100) and reviews of the literature of primary systemic amyloidosis,[1-14] we found no report of similar bone marrow findings though Snapper, Turner and Moscovitz [15] have reported Russell bodies in the bone marrow in atypical amyloidosis accompanying multiple myeloma. Morphologically, amyloidosis associated with multiple myeloma and the so-called primary systemic amyloidosis are quite similar except for the presence of myeloma cells in the former disease. Organs of mesenchymal origin are involved in both types, and the heart is the organ most frequently involved in both. In the present case report, no clinical or pathologic evidence of myelomatosis or plasma cell hyperplasia existed. Amyloidosis has long been considered to be a product of or related to plasma cells and, if this is true, the finding in this case of Russell bodies, which are likewise considered a product of plasma cells, may constitute a further link between paramyloidosis or atypical amyloidosis associated with myeloma and primary amyloidosis of unknown etiology in which there is no recognized increase in plasma cells. An additional possibility is that this case might well have been one of unrecognized plasma cell proliferation at an earlier date in which the proliferation had subsided (burnt out) prior to death, as has been suggested by Ehrich.[16]

Case Report

A 56 year old white male was admitted to Walter Reed Army Hospital in September, 1953, at which time his chief complaints were exertional dyspnea, orthopnea and edema of the lower extremities. About one year previously, when he first began to have exertional dyspnea, he was found to have an abnormal electrocardiogram and was hospitalized for study in a military hospital in Germany, where he was on duty. During that hospitalization his general and cardiovascular findings were

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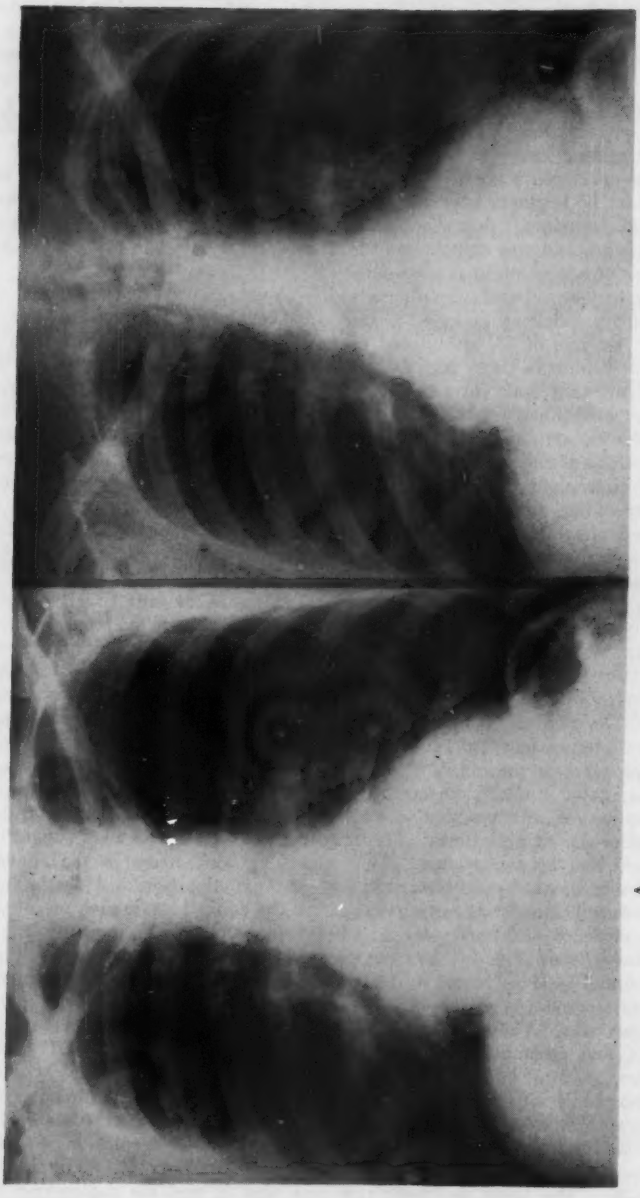
normal except for the abnormal electrocardiographic findings, an abnormal roentgenogram of the chest, which revealed definite cardiac enlargement of "left ventricular configuration," and an eosinophilia of 10%. The blood pressure was normal at that time and had not been known to be elevated in the past. A diagnosis of arteriosclerotic heart disease was made during that short hospitalization. He was discharged without any specific cardiac therapy, and recommendations were given to follow a low fat diet. In January, 1953, nine months prior to his death, he first noted mild intermittent ankle edema during a mild six-day illness diagnosed as "influenza." Following this he developed a nonproductive cough with frequent wheezing in his chest. Six months later he began to have an increase in the peripheral edema and associated periods of mild orthopnea. A low sodium diet was prescribed, with little effect. He continued his work and was ambulatory at the time he returned to the United States and at the time of admission to this hospital.

The past history revealed diphtheria in childhood, an episode of typhoid fever at the age of 10, influenza at age 13, and jaundice at age 26, all without known sequelae. At the age of 28 he suffered chemical burns of the face and neck, with extensive cicatrization in those regions. The family history revealed that one sister had diabetes and that both parents lived to an advanced age but died of terminal cardiovascular conditions.

Physical examination revealed a slender, middle-aged white male whose weight was 155 pounds and whose height was 69 inches. There was an extensive, partially unpigmented cicatrix of the face and anterior neck regions, with some retractions and deformity of the external ears and mild retraction of eyelids. The neck veins were engorged and distended when the patient was in a sitting position. Marked pitting edema was present in the feet and legs and extended up to the abdominal wall and gluteal regions. Minimal cyanosis of the stasis type was present. The lower border of the liver was easily palpable 3 cm. below the costal margin but was smooth and nontender. The ocular fundi were normal, without evidence of vascular changes. The blood pressure taken from the right arm and in the supine position was 120/70 mm. Hg. The heart rate was regular but rapid, with a rate of 120 per minute, and a well heard gallop rhythm of the diastolic ventricular type was audible at the apex. No cardiac murmurs were audible, and the heart sounds were normal except for a moderate accentuation of the second sound at the pulmonary valve area. Moderate dyspnea was present, and moist crepitant râles were noted in both lung bases. Fluoroscopic study of the heart revealed an enlarged cardiac silhouette, with the configuration of left ventricular and atrial enlargement, and with decreased amplitude and vigor of pulsations. There were no associated findings suggestive of pericardial effusion or constriction. The venous pressure taken in the antecubital vein was 200 mm. of water, and the arm-to-tongue circulation time with Decholin (H) was 25 seconds. The physical findings confirmed the clinical impression of congestive failure with evidence of both right- and left-sided weakness.

Laboratory Data: The erythrocyte count was 5,000,000 per cubic millimeter; leukocyte count, 10,400 per cubic millimeter, with a differential of 65% neutrophils, 34% lymphocytes and 1% eosinophils. The sedimentation rate was 2 mm. per hour (Wintrobe method). The total serum protein was 7 gm.%, with a serum globulin of 3.3 gm.% and albumin of 3.7 gm.%. The serum chloride was 117 mEq./L.; serum sodium, 142.3 mEq./L.; serum potassium, 5.0 mEq./L.; calcium, 5.3 mEq./L.; inorganic phosphorus of the serum, 3.2 mEq./L. The serum carbon dioxide combining power was 51.9 vol.% and the urea nitrogen was 16 mg.%. The serologic test for syphilis was negative. The urine specific gravity varied from 1.005 to 1.010, a trace of albumin was found on one examination, and the microscopic findings were not remarkable. The basal metabolic rate was plus 5, and the radioactive uptake was 55% (normal in this laboratory, 20 to 40%). The roentgenogram of the chest



A B

FIG. 1. A. Chest x-ray, December 8, 1952. B. Chest x-ray, September 22, 1953, at time of admission to Walter Reed Army Hospital.

on September 22, 1953, revealed a moderately enlarged cardiac silhouette (cardiothoracic ratio was 30% above normal), with a configuration of predominant left ventricular hypertrophy, and the lung fields showed bilateral pulmonary edema (figure 1A). Upright and supine views in posterior-anterior and lateral views revealed no contour changes suggesting pericardial fluid. Review of previous chest roentgenograms taken elsewhere in 1952 (figure 1B) showed evidence of a lesser degree of cardiac hypertrophy at that time but essentially the same cardiac configuration. An electrocardiogram taken elsewhere on February 14, 1953 (figure 2A), was considered definitely abnormal, the outstanding abnormalities being (1) low amplitude of all complexes in the bipolar and unipolar limb leads and less so in the precordial leads; (2) widespread T wave abnormalities with negativity in all limb leads except

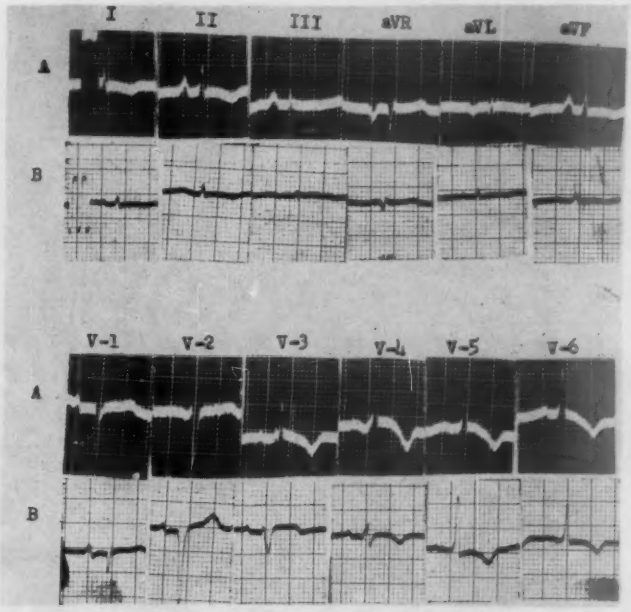


FIG. 2. A. Electrocardiogram taken February, 1953. B. Electrocardiogram taken September 22, 1953.

aVR, were abnormally positive and negative in V_3 to V_6. A tracing taken in December, 1952, was located and it was similar. The tracing taken at the time of admission to this hospital was similar (figure 2B), the only significant changes being a greater decrease in voltage of all complexes. The transition zone had shifted further to the left, suggesting increase in dilation of the right heart. No Q waves were seen in V_6 in either tracing, but leads were not taken in more lateral positions. The QRS duration and PR intervals were normal, without other evidence of a specific conduction defect. The abnormalities were considered nonspecific and nondiagnostic, but were interpreted as indicating widespread myocardial disease.

Course in Hospital: A period of five days was spent in the hospital for the purpose of establishing the etiology of the cardiac hypertrophy and failure and of insti-

tuting therapy for the myocardial insufficiency. The patient responded promptly and remarkably to sodium restriction, digitalis and mercurial diuretics, with a weight loss of 16 pounds, and relief of peripheral edema, dyspnea, and cough. The etiology of his heart disease was not evident from this brief period of observation and study, but it was considered to be of some obscure etiology rather than arteriosclerosis. He was released from the hospital on the fifth day to make an important trip to Texas, with plans to be re-admitted to the hospital one week later, on return, or to continue further diagnostic studies as an out-patient. He maintained his improvement during the 12 days of absence from the hospital, but died suddenly in an office in the Pentagon Building on October 9, 1953. Although the Medical Examiner had released the body with a death certificate of "coronary occlusion," permission was obtained to perform an autopsy after the body had been embalmed, as it was not felt that this patient had had simple arteriosclerotic heart disease.

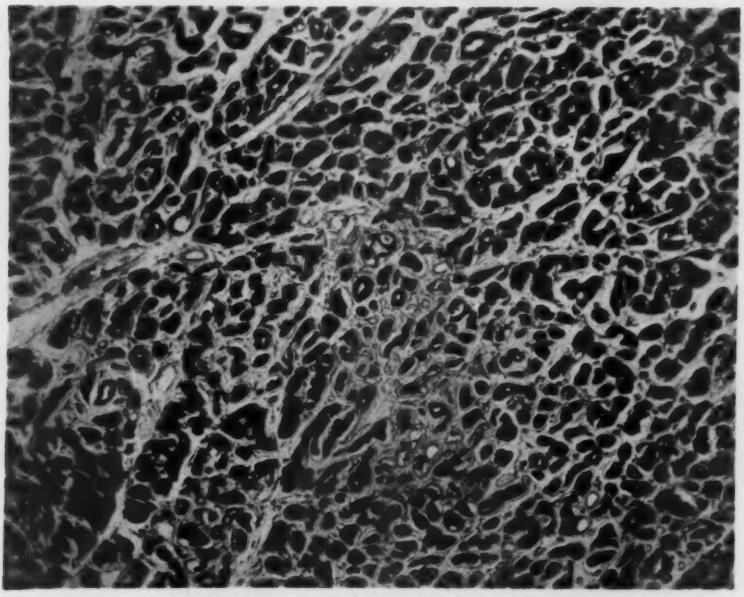


FIG. 3. Section of myocardium (100×) showing amyloid deposits.

Necropsy Findings: At autopsy the heart was enlarged, weighing 675 gm. The epicardium and endocardium, including the cardiac valves, were not unusual. The muscular walls of all chambers of the heart were thickened, and the cut surface of the myocardium had a glistening, semitranslucent appearance. Microscopic study of the heart (figure 3) revealed an extensive deposit of hyaline eosinophilic material which stained positively for amyloid in the walls of the arteries. This material obscured the details of individual muscle fibers in the arterial walls and was interpreted as amyloid. Amyloid was also abundantly present between myocardial fibers.

Amyloid was noted in the walls of the arteries of all organs. In the liver the arteries of the portal spaces were extensively involved, but no amyloid was present beneath the endothelium of the sinusoids. Histologic details of the walls of the splenic

arteries were obscured by amyloid, and large deposits of this material were present in the splenic pulp and encroached upon the scant lymphoid follicles. The trabeculae also showed deposits of amyloid. The walls of the arteries of the kidney contained amyloid, but the other components of these organs, including the glomeruli, were unaltered. The arteries of the bone marrow, periadrenal fat, striated muscle, intestine, pancreas, testes, prostate, and bladder in particular showed heavy deposits of amyloid. In the adipose tissue (figure 4) rings of amyloid were noted about fat cells. This was most pronounced in the periadrenal, peripancreatic, and epicardial adipose tissue. In sections from the psoas muscle, small deposits of amyloid were present between muscle fibers. The smooth muscle of the intestine and urinary bladder showed large deposits of amyloid.

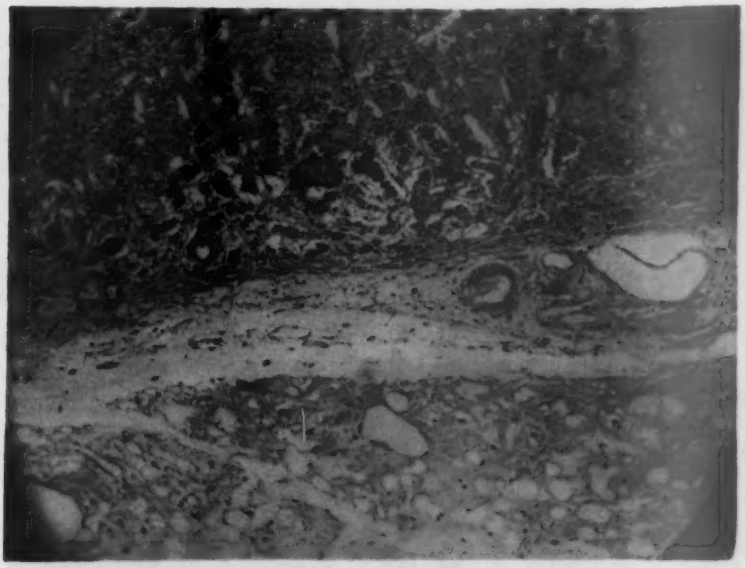


FIG. 4. Section of adrenal cortex (100×) showing deposits of amyloid in periadrenal fat. The fat cells in this instance have a ringlike appearance.

In the bone marrow (figure 5) there were large numbers of round hyaline bodies. In instances, a thin rim of cytoplasm containing a small nucleus was situated eccentrically on one side of these bodies. These structures measured up to 40 μ in diameter and were considered to be Russell bodies. They did not stain positively for amyloid. There was only minimal arteriosclerosis of the coronary arteries, and there was no evidence of occlusion or of myocardial changes from a recent or old infarction. The central nervous system in this case was not examined, due to limitations in the autopsy permission.

DISCUSSION

Nature of the Cardiovascular Findings: It is believed that this patient died of amyloidosis of the heart. It was considered to be the cause of the congestive

failure, and the sudden death probably resulted from an acute ventricular arrhythmia. Involvement of the heart may occur with amyloidosis associated with multiple myeloma or primary systemic amyloidosis, or the amyloid may be restricted entirely to the heart in a condition which Thomashow et al.[18] termed primary cardiac amyloidosis. Pruitt [9] points out that amyloid deposits restricted entirely to the heart usually occur in patients of 70 years or more. In recent years there has been increasing evidence that strict compartmentalization of amyloidosis into primary systemic, primary cardiac, amyloidosis secondary to chronic infections, and paramyloidosis associated with myeloma may not be justified. Jackson [17] does not consider either primary or secondary amyloidosis as separate entities, but considers both to be manifestations of a hypersensitivity

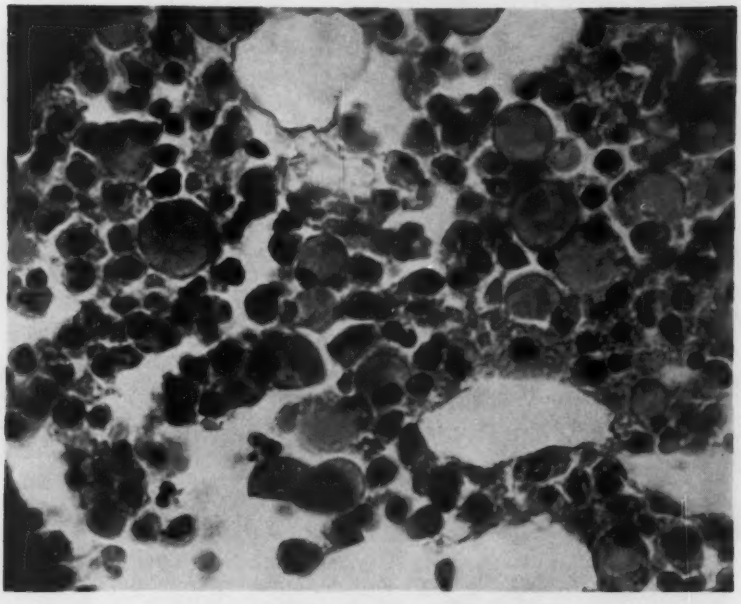


FIG. 5. Bone marrow (500×) sections showing numerous Russell bodies.

disease. If, however, one adopts the usual classification of amyloid disease, the case which we are reporting appears to belong in the category of primary systemic amyloidosis. Lindsay,[3] in reviewing 22 cases of primary amyloidosis, noted that nearly one-half of the cases had cardiac decompensation. In reporting on the frequency of various clinical manifestations of primary amyloidosis, Higgins and Higgins [5] list cardiac failure as most common, as follows: congestive heart failure, 56%; general muscular weakness, 50%; amyloid involving the skin and buccal mucosa, 35%; lymphadenopathy, 27%; pain in the extremities, 24%; weight loss, 40%; macroglossia, 40%; dysarthria with macroglossia, 33%; dysphonia with macroglossia, 25%; hypertension, 20%; purpura, 15%; abdominal pain, 12%; pruritus, 7%; epistaxis, 5%; fever, 5%; hematemesis,

4%; history of allergy, 3%. Congestive failure was the only symptom noted in the patient reported, and while the primary involvement was that of amyloid in the myocardium and its blood vessels, there were deposits in the musculature of blood vessels elsewhere in the body. The possibility of primary systemic amyloidosis was considered by one of us (T. W. M.) in the differential diagnosis of the obscure cardiac hypertrophy and failure in this patient, and led to our persisting in efforts to obtain autopsy material from the embalmed body. It is doubtful if the antemortem diagnosis could have been definitely established beyond the suspicion stage had the patient returned for the planned diagnostic studies. The electrocardiographic abnormalities indicated widespread disease. Although the changes were similar to those described by others,[18-19] they were not diagnostic. The Congo red test might have been diagnostic, although this test is less reliable in primary amyloidosis than in secondary amyloidosis. It is a conjecture whether this is always due to a lessened affinity for Congo red in primary systemic amyloidosis, or is a reflection of the relatively small quantity of amyloid present in the liver. Biopsy of the skin, skeletal muscle, tongue or even the liver might have been diagnostic. Selikoff and Robitzer [20] have emphasized the values of gingival biopsy in secondary amyloidosis, although there is no record of its employment in primary amyloidosis. King [21] has observed that special silver stains may demonstrate amyloid in atypical amyloidosis.

Actually, one might expect such a procedure to be more helpful in primary systemic amyloidosis, since amyloid is prone to involve blood vessels and mesenchymal elements in general in this condition.

Nature of Amyloid: Amyloid has been recognized for more than a century,[22] yet the exact pathogenesis of this material is still incompletely understood. However, many facts which are undoubtedly related to its etiology have been elucidated, and suggest that the various chemically and morphologically recognized types are closely related. The separation into such chemical and morphologic types as described in the past [1, 22-26] may not be valid. Amyloid has been produced experimentally by a variety of means, including injections of turpentine, sulfur, human sera, sodium caseinate, various bacteria and multiple vaccines.[27-33] Hass [34] identified two slightly different protein fractions and a sulfate fraction in amyloid of secondary amyloidosis. It was concluded that the protein matrix becomes a complex substance by combination with other substances.

Certainly there is now good evidence that amyloidosis is in some ways related to plasma cells.[15, 35, 43] Teilum [44] has drawn attention to the coincidence of hyperglobulinemia and paramyloidosis, and pointed out the direct relation of these factors to an increase in the number of plasma cells. Magnus-Levy [45] has presented strong evidence that amyloid occurring in cases of multiple myeloma is produced by plasma cells. He points out that amyloid is found in large quantities in intraosseous myeloma tumors which have undergone pressure necrosis, and cites the work of Herbut and Erf, with that of Bayrd and Bennett [46] in finding amyloid within myeloma cells as support of his contention. Morphologically, amyloidosis accompanying multiple myeloma and primary systemic amyloidosis are quite similar except for the presence of myeloma cells in the former condition. Propp, Scharfman, Beebe and Wright [42] have reported a case of atypical amyloidosis associated with nonthrombocytopenic purpura and plasma cell hyperplasia of bone marrow. In this case it was difficult to deter-

mine whether multiple myeloma was present, although foci of plasma cells remained. Bayrd and Bennett [46] showed that amyloid may be found within the plasma cells, and since these cells are not considered phagocytic, its origin within the plasma cell must be presumed. All forms of secondary amyloidosis seem to be related to antibody production, as is indicated by its experimental production in response to a variety of antigens and its occurrence in chronic diseases. Fagraeus [47] and other investigators [48-49] have clearly demonstrated that plasma cells may produce antibodies, and Bing and Plum [50] have compared various conditions in which hyperglobulinemia occurs and found plasma cell increases a common factor. Barr [51] suggests that myeloma itself may represent an immune response to an unknown antigen, and cites reports of cases of trichinosis [52] and of sulfonamide hypersensitivity [53] as evidence of myeloma-like syndromes produced by known antigens. Wolf and Worken [54] reported a case presenting the triad of amyloidosis, hyperglobulinemia, and bone marrow plasmocytosis in the apparent absence of findings of multiple myeloma at autopsy. During life the presence of myeloma-like cells had been certified by numerous competent observers, and this transient phase of plasma cell hyperplasia as noted in the bone marrow studies during life was attributed to hypersensitivity to a sulfonamide drug. Amyloid may well represent a family of substances produced by plasma cells in response to a variety of antigens. While amyloid associated with chronic infections is now infrequent, the experimental work of Teilum,[55] demonstrating the marked enhancement of amyloid formation in experimental animals which are concomitantly given cortisone; and the inhibitory effects of ascorbic acid on this process, is exceedingly interesting. Perhaps with the widespread clinical usage of steroids, amyloidosis will be seen with increased frequency in the future.

Nature of Russell Bodies and Their Relationship to Plasma Cells and Amyloidosis: Russell bodies are peculiar cytoplasmic inclusions described as occurring in the cytoplasm of cells. They are acidophilic in their staining characteristics; with Romanowsky's stain they appear red, and stain blue with Weigert's stain. The origin and chemical nature of these bodies are not entirely known. It is interesting that Russell,[56] who first described them, considered such bodies as the "characteristic organism of cancer." Generally, they are considered to have a high protein content. Pearse,[57] in his study of the nature of Russell bodies and Kurloff bodies, concluded that Russell bodies consisted of a mucoprotein. They are ordinarily considered as being peculiar to the plasma cells, and Downey [58] regards them as pathologic secretions found in parent plasma cells, and feels that such bodies are liberated into tissues following death of the parent cells. Recently Rappaport and Johnson [59] described the finding of intracytoplasmic inclusions resembling Russell bodies tinctorially, histochemically and, to a varying degree, morphologically, in cells of malignant lymphomas from patients with associated acquired hemolytic anemia. It is of interest that the three patients described by these authors were from a group of eight who had a positive Coombs' test during life, and in two of the three, the autoagglutinin titers were unusually high (1 : 8,096 and 1 : 25,600, respectively). One of the two also had abnormally high serum globulin levels with cryoglobulinemia. They suggested that the presence of such Russell body-like material in the neoplastic cells may be the morphologic manifestation of protein synthesis by these

cells, and that these abnormal proteins may play an important part in the immunologic mechanisms responsible for the development of the acquired hemolytic anemia in association with malignant lymphomas. These and other observations suggest that Russell bodies, like amyloid, may be a manifestation of hypersensitivity. The presence of systemic amyloidosis and Russell bodies in the patient in this case report strongly suggests the probability of myelomatosis, in spite of the absence of other clinical or autopsy findings to support such diagnosis. Snapper et al.,[15] in reporting detailed findings of 11 patients with multiple myeloma complicated by amyloidosis, pointed out the relative rarity of bone lesions on roentgen examinations in these patients. Five of the 11 patients with paramyloidosis reported by them had no recognizable areas of bone destruction, and only one of the five had had significant bone pain during life. They likewise pointed out that hyperglobulinemia is rare in patients with myeloma who develop amyloidosis. Only one of the 11 had a serum globulin above 2.5 gm.%. Our patient's serum globulin was 3.3 gm.%. In this respect the findings differ from amyloidosis produced under experimental conditions where hyperglobulinemia is frequent. Apitz [60] has suggested that, in myeloma patients who develop amyloidosis, the abnormal globulins, instead of circulating in the blood, are deposited in the tissues as paramyloid. Bence Jones protein was present in the urine in 10 of the 11 patients reported by Snapper, and might have been found in our patient had special examinations been made. In instances where multiple myeloma complicated by amyloidosis occurs without demonstrable lesions in the roentgenogram or the presence of bone pain, the incidence of extensive cardiac involvement and death by severe congestive failure is high, five of the eight having at autopsy presented amyloid infiltration of the heart. It is of great interest that one of these cases demonstrated conspicuous Russell bodies in the bone marrow, similar to those in this case report. Wallerstein [61] has stressed the importance of investigating every case of so-called primary amyloidosis for the presence of myelomatosis. Apitz [60] states that, even though such careful examination does not reveal myeloma, it might develop if the patient lives long enough. A review of all available roentgenograms of our patient revealed no evidence of bone lesions in the films as taken, but a complete skeletal survey was not made, either by roentgenogram or at autopsy. A bone marrow examination was not made during life, and there was no plasma cell hyperplasia of the bone marrow or other tissues at autopsy to establish a clinical or postmortem diagnosis of multiple myeloma. However, the occurrence of Russell bodies, a recognized degenerative product of plasma cells, in an otherwise typical case of primary amyloidosis such as we are reporting, is considered to constitute a possible link between cases showing atypical amyloidosis or paramyloidosis with increase of plasma cells, as in multiple myeloma, and those in which there is no evident increase in these cells and which are classified as primary systemic amyloidosis.

Summary

1. An additional case of cardiomegaly and cardiac failure is reported in which the autopsy findings were those of primary systemic amyloidosis with extensive involvement of the hearts and blood vessels.

2. The presence of numerous Russell bodies in the bone marrow of an otherwise classic primary systemic amyloidosis suggests the possibility that this case represents the link between those cases of paramyloidosis in which plasma cell hyperplasia is evident, as in multiple myeloma, and those in which it is not, as in primary systemic amyloidosis. The presence of Russell bodies in this case is considered quite consistent with the idea that plasma cells may be the common denominator in the pathogenesis of all amyloid disease.

SUMMARIO IN INTERLINGUA

Iste reporto concerne le caso de un masculo de 56 annos de etate qui presentava un problema diagnostic de cardiomegalia e disfallimento myocardial de etiologia incognoscite e in qui amyloidosis systemic primari esseva le principal constatation necroptic. De interesse esseva etiam le presentia de numerose corpores de Russell in le medulla ossee. Un simile constatation ha essite reportate per altere autores in casos de paramyloidosis associate con myeloma multiple.

Le subjecto del presente reporto exhibiva nulle lesiones demonstrabile in le systemas skeletal que haberea potite indicar myeloma, e su caso non esseva characterisate per un augmento del globulina seral. Proque corpores de Russell es considerate como productos degenerative de cellulas plasmatic, il pare justificate stipular que le presente caso es un caso de non-recognoscite proliferation de cellulas plasmatic a un tempore precoce e que iste proliferation habeva cessate ante le morte. Le datos suggere que il existe un connexion inter le si-appellate "classic amyloidosis primari" e paramyloidosis associate con "classic myeloma multiple" e que un anormalitate del cellulas plasmatic es possibilemente le denominator commun del pathogenese de omne morbos amyloide.

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CHRONIC SUBPHRENIC ABSCESS DUE TO *SALMONELLA ORANIENBURG* INFECTION: CASE REPORT AND REVIEW OF LITERATURE*

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This is a report of a case occurring in a physician of chronic subphrenic abscess due to the organism *Salmonella oranienburg*. The case is of interest not only because no similar report has been found in the literature but also because of the chronicity of the lesion and the difficulty in establishing the diagnosis. The correct diagnosis was not made until an exploratory laparotomy was performed one year after the onset of symptoms.

S. oranienburg was first isolated by Kauffmann [1] in 1930, from the stool of a healthy boy living in an institution in Oranienburg, Germany. The salmonella are gram-negative, nonspore-forming, motile bacilli, easily cultivated on ordinary culture media. They characteristically produce acid and gas in dextrose and maltose, but do not ferment lactose, salicin or sucrose. They also produce hydrogen sulfide, but not indol, and they do not liquefy gelatin. The different species are closely related antigenically, and these relationships are used as the main criteria in classification. Our knowledge has been increased since the introduction of a schema of classification by Kauffmann and White [2] based on antigenic analyses, by means of which more than 220 species of salmonella have been identified. They are at present classified into nine groups, to which further groups and new types have been added, depending on their biochemical and serologic reactions, the latter being based on agglutination tests with sera against the somatic and flagellar antigens of the organisms. According to the Kauffmann and White classification, the antigenic formula of *S. oranienburg* is found in group C and consists of O antigen VI_1, VI_2, VII and H antigens, Phase 1, m and t. Pathogenetically, it is grouped with those salmonella organisms which produce disease in man as well as in birds and animals. This organism has been frequently isolated from chickens,[3] turkeys [4] and dried egg products,[5] and is a natural cause of epizootics in quail.[6] From a survey of the literature [4, 7, 8, 9, 10, 11, 12, 13, 14] it would appear that *S. oranienburg* is responsible for a relatively small proportion of the clinical infections due to the various species of the salmonella group. The reported incidence of *S. oranienburg* infection varied between 1.9% and 24%, averaging 8.7%.

It is now generally recognized that systemic infection with organisms of the salmonella group is not a rare occurrence. The literature is replete with reports of cases involving almost every system of the body. Most of the cases are of the acute toxic type, with severe constitutional reactions, and the patients are chiefly the very young and old, the majority infants and children. Gen-

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eralized infection by salmonella organisms may assume a much more protean form than was thought by earlier writers. Three clinical types of infection are now generally recognized. The first is salmonella gastroenteritis, which is characterized by a short incubation period, followed by an explosive febrile illness with diarrhea. Although all the serologic groups may cause this syndrome, *S. typhimurium* is the most common agent. The second clinical type is salmonella fever, similar to the clinical picture of typhoid fever and usually caused by *S. paratyphi A* and *B*. Infection with *S. paratyphi A* is marked by fever and bacteremia, but usually no enteritis, while infection with *S. paratyphi B* produces fever and enteritis, and occasionally other visceral disease. The third clinical type is salmonella septicopyemia, usually caused by members of the C serologic group, particularly by *S. choleraesuis*. There is marked invasiveness with *S. choleraesuis*, approximately 60% having a positive blood culture, with a tendency to develop visceral localizations. The tendency to develop visceral localizations is considerably less with *S. oranienburg* infection. The clinical manifestations may thus run the gamut from mild to severe gastroenteritis, with or without septicemia. At times the presenting syndrome simulates typhoid fever, and occasionally a localized inflammatory process occurs.

Salmonella infection may localize anywhere in the human body. The occurrence of abscess or other localized infection is, however, relatively uncommon. Human infections from which *S. oranienburg* has been cultured include gastroenteritis,[4, 7, 15] pneumonia,[7] pneumonia and pleurisy,[16] pneumonia and empyema,[17] septicemia without endocarditis,[18] endocarditis,[19] meningitis,[7, 20, 21] cholecystitis,[7, 15] perirectal abscess,[22] abscess of the buttock,[7] appendicitis [7] and osteomyelitis.[7, 15, 33] No case of subphrenic or liver abscess caused by *S. oranienburg* was found in a review of the literature. The occurrence of subphrenic abscess caused by other salmonella organisms is extremely rare. In an analysis of 3,372 collected and personal cases of subphrenic abscess reported by Ochsner and Graves,[23] none was caused by salmonella infection. Hochberg,[24, 25] in two separate reports on 111 and 139 cases of subphrenic abscess, found no instance of salmonella infection. Faxon,[26] in a report of 111 consecutive operative cases of subphrenic abscess, reported no cases due to salmonella infection. There are, however, several cases of subphrenic abscess recorded in the literature resulting from infection by salmonella organisms other than *S. oranienburg*, but none with a chronic course as herein described. Walker [27] reported a case of transient bacteremia followed by a metastatic splenic abscess with secondary extension into the left subphrenic space. The illness was characterized by fever, chills, diarrhea, and left lower chest and shoulder pain. The abscess was drained and *S. choleraesuis* isolated by culture. Sachs [28] reported a case of acute *S. choleraesuis* septicopyemia with autopsy findings of confluent bronchopneumonia, abscess of the right lung, subphrenic abscess, and abscesses of the liver, spleen and brain. The patient was ill for one month and had a positive blood culture for *S. choleraesuis* and negative stools. Davies [29] reported a case of subphrenic abscess and left pleural effusion with *S. dublin* cultured from both the blood and abscess material. There was no history of enteritis, and the stools and urine were negative for salmonella. Chloramphenicol was given and the abscess subsided without surgical intervention. In a clinical report by Saphra [30] on the evaluation of 329 infections caused by *S. choleraesuis* and identified in the New York Sal-

monella Center, there were 163 cases of septicemia, with localized manifestations of abscess and focal inflammation in 43 cases, and one case of subphrenic abscess. No details were given concerning the case of subphrenic abscess. Cases of subphrenic abscess caused by salmonella are rare, therefore, and the occurrence of a chronic subphrenic abscess has not been found in the literature. "Cold abscesses" may occur, however, following typhoid fever, and chronic salmonella abscesses are occasionally recorded in bone[8, 30, 31, 32] and cartilage.[33] This is exemplified in a report by Brock [34] of a case of *S. paratyphi B* costal chondritis with intrachondral abscess which occurred 14 years after an attack of gastroenteritis. The patient was cured by radical excision of the diseased cartilage.

Case Report

A 45 year old male physician had been well until August 18, 1951, when he complained of localized, recurrent, stabbing right upper quadrant pain lasting 15 to 30 seconds. The pain awakened him and disturbed his sleep but was not severe enough to be incapacitating. Slight localized tenderness was found in the gall-bladder region. He was afebrile and the pain subsided in about five days, leaving residual discomfort. X-ray and fluoroscopy of the chest, cholecystogram and gastrointestinal series were negative. The blood count, blood cholesterol, cephalin flocculation, thymol turbidity and icterus index were normal. The sedimentation rate was 15 mm. per hour.

On September 17 the pain suddenly recurred, with gradually increasing severity, related to respiration and body movement and requiring codeine and aspirin for relief. The patient had difficulty in sleeping on the left side because of pain, and there was also considerable distress on the right side, though to a lesser degree. He also complained of generalized myalgia, most marked in the extremities, especially in the region of the insertion of the right deltoid muscle. There was no shoulder, joint or back pain. From September 17 to the day of admission to the hospital (October 3), he had a daily, low grade fever up to 100.6° F. orally, accompanied by chilliness and profuse night sweats. He complained of dull pain in the right lower anterior chest and right hypochondrium. He was given a total dose of 4.5 gm. of oxytetracycline (Terramycin) for five days, followed by a total dose of 5.5 gm. of chloramphenicol (Chloromycetin) for five days, without clinical improvement.

The past history revealed that the patient had had an acute streptococcic pharyngitis in 1933, followed by a low grade fever for a period of six months. While on a trip to Rio de Janeiro in 1940 he had had an acute enterocolitis, characterized by severe toxemia, chills, fever of up to 104° F., and profuse diarrhea, which subsided spontaneously in five days. The stools were not cultured. He had had an acute posterior myocardial infarction in August, 1948, with uneventful recovery and no subsequent coronary insufficiency. During the two months prior to the onset of the present illness he had two transient attacks of auricular fibrillation, which terminated spontaneously after two and three hours, respectively.

He was admitted to the hospital for further observation, and physical examination revealed approximately 25% lag of the right chest on inspiration, with point tenderness in the seventh intercostal space in the right anterior axillary line. There was slight tenderness on palpation under the right costal margin in the midclavicular line. Several observers heard a friction rub in the right anterior chest. During this period of hospitalization he had a daily fever as high as 102.4° F. rectally. He appeared acutely ill and toxic. The pain increased in intensity, becoming constant, severe and present in all positions. He also developed paroxysms of lancinating pain in the right upper quadrant, during which he would sit up suddenly and cry out

because of pain. Numerous measures were attempted for relief of pain, including the administration of codeine, Demerol, x-ray therapy consisting of 75 r over the anterior and posterior chest for two consecutive days, local procaine infiltration, and local intercostal nerve block (injecting T-6, T-7 and T-8 with Intracaine). The pain became increasingly severe on October 12, despite the use of 100 mg. of Demerol every three to four hours. It was therefore decided to administer 300 mg. of cortisone intramuscularly, followed by 200 mg. the following day. There was marked improvement within 12 hours, and the patient slept well and comfortably the following night. The pain disappeared within 48 hours. He continued on gradually decreasing doses of cortisone by mouth for 10 days. During this period of hospitalization several blood counts were normal, with sedimentation rates ranging between 16 mm. and 26 mm. per hour. Various liver functional tests were normal. Agglutinations for paratyphoid A and B, typhoid O and H, brucellosis and OX 19 were negative. Three blood cultures and complement fixation tests for amebiasis, Q fever and psittacosis were negative. Three stool examinations were negative for ova and parasites. Spinal fluid examination was normal. An electrocardiogram showed an old posterior myocardial infarction.

The clinical syndrome appeared bizarre to the examining physician and to numerous consultants. The attending physician suggested the diagnosis of infectious neuronitis. The neurologic consultant, however, disagreed and made a diagnosis of epidemic pleurodynia. The possibility of an amebic liver abscess was also considered by the attending physician, and the patient was given a course of chloroquine, with a total dose of 11 gm. over a period of 20 days. He was discharged from the hospital on October 14. The low grade fever subsided three days later, the appetite improved, and he returned to work in two weeks.

During the following year the patient had occasional twinges of right upper quadrant pain but continued to work. A number of blood counts were within normal limits, although several repeated sedimentation rates were slightly elevated, varying between 12 and 23 mm. per hour. Additional stools showed no amebae or other parasites.

On October 8, 1952, the patient again complained of severe right lower chest pain, aggravated by lying on the right side. He was most comfortable in the supine position. He first noted fever on October 10, and during the following three weeks the temperature averaged between 99° F. and 100° F., the highest reading being 102° F. He complained of mild generalized muscle aching and night sweats. The pain persisted, and on some occasions he felt point tenderness in the seventh intercostal space in the anterior axillary line and soreness in the right shoulder. X-ray and fluoroscopic examination of the chest showed that the diaphragms moved equally and synchronously with respiration. The right diaphragm was not elevated and the costophrenic sinuses were clear. Intravenous urography and barium enema were normal. Although there was no x-ray evidence of elevation of the right diaphragm, the possibility of a liver abscess was again entertained and a second trial of antiamebic therapy was instituted. He was given a total dose of 14 gm. of oxytetracycline over a period of seven days, and 6 gm. of chloroquine over a period of 10 days, with no significant clinical effect. It was the consensus that no definitive diagnosis was possible without exploratory surgery.

The patient was re-admitted to the hospital on November 7, and on the following day the abdomen was opened through a right subcostal incision. About three inches from the free edge of the liver the diaphragm was densely adherent to the liver. These adhesions were divided by sharp dissection and a large fluctuant mass was found adherent to the diaphragm and anterolateral chest wall. This was opened and approximately 100 c.c. of purulent material were evacuated. A portion of the roof of the abscess was excised. On digital exploration the walls of the abscess were thick

and there was only one palpable cavity. A small area of liver, measuring approximately 4 cm. in diameter, was involved and this was excised. Bleeding was controlled by placing several sutures in the liver. A Penrose drain was placed in the abscess cavity and brought out through the lateral edge of the incision.

Microscopic sections of the liver revealed fibrous tissue in which there were occasional nodules of liver parenchyma. The fibrous tissue was studded with small abscess cavities lined by granulation tissue and showing various degrees of infiltration by lymphocytes, histiocytes, plasma cells and, in a few places, leukocytes. Sections of the abscess wall revealed that it was lined by granulation tissue showing cellular infiltrations similar to that seen in the liver. In some areas numerous foamy histiocytes infiltrated the wall. Behind the granulation tissue was a dense fibrous capsule, and portions of the wall showed many leukocytes. Culture from the abscess material revealed *S. oranienburg*. The organism showed the following order of sensitivity: oxytetracycline, chloramphenicol and Aureomycin, with resistance to penicillin, streptomycin and bacitracin.

The immediate postoperative course was stormy. The patient became toxic and septic, with fever of up to 103° F. during the first 10 days, gradually subsiding to a low grade fever between 99° F. and 100° F. until discharge from the hospital. During the first postoperative week he had frequent severe diaphragmatic spasms characterized by sudden momentary attacks of pain, uncontrolled by frequent narcotics (administered as often as every three hours). These attacks gradually subsided during the second week. He was given 28 gm. of oxytetracycline over a period of two weeks, and 9 gm. of chloramphenicol over a period of one week. Occasional premature ventricular contractions were noted postoperatively, and on November 21 frequent runs of premature ventricular beats occurred. These were controlled with quinidine. X-rays of the chest on November 11 and 25 showed the heart at the upper limits of normal size, and the lungs clear, with no evidence of fluid or atelectasis at the right base. Special views of the right lower ribs failed to demonstrate evidence of osteomyelitis. The white blood count increased to 13,400, with 71% polymorphonuclear cells and 16% nonsegmented forms, one week following surgery, and later returned to normal. Blood cultures were negative. Several cultures from the wound drainage were positive for *S. oranienburg*. The patient was discharged from the hospital 18 days postoperatively, on November 26, with a low grade fever, marked debility, a 15 pound weight loss and a positive culture for *S. oranienburg* from the discharge of the residual sinus tract.

During the following 20 days at home he continued to have a low grade fever (up to 100° F.), with generalized aching, night sweats and vague right upper quadrant and anterior chest pain. The sinus tract continued to drain. He remained on oxytetracycline, taking a total of 52 gm. During the five days prior to re-admission to the hospital on December 23, he complained of intercostal tenderness over the area of the abscess, right shoulder pain with deep inspiration, and tenderness just below the right costal margin. The urinalysis and blood count were normal. X-ray of the chest revealed a normal right diaphragm, moving with respiration, and no evidence of pleural fluid.

He was taken to surgery on December 24, and an incision was made in the right anterolateral chest wall over the ninth costal cartilage. The costal cartilage and a portion of rib were excised and a normal diaphragm was visualized for about 2 inches. Above this point, by blunt dissection, the finger entered an abscess cavity containing about 100 c.c. of thick purulent material. The abscess cavity was about 3 inches in diameter, with the walls thick and indurated. The costal arch was cut to make the opening larger, a de Pezzer catheter placed at the top of the cavity and the cavity packed with gauze. Culture of the pus was positive for *S. oranienburg*. The abscess cavity was irrigated with oxytetracycline solution every four hours for the following

week and the pack removed and replaced with vaseline gauze on December 30. The patient became afebrile on the fourth postoperative day, showing considerable clinical improvement, and was discharged on December 31, 1952. During January, 1953, the cavity gradually closed and irrigations were discontinued on January 14. The temperature remained below 99.2° F. After the twenty-first postoperative day it remained normal. He returned to work on February 3.

In early September, 1953, a small abscess in the abdominal incision was drained and showed a positive culture for *S. oranienburg*. On October 9 pain recurred in the right anterior chest in the region of the postoperative site, aggravated by deep breathing and bowel movements, and referred to the right shoulder. Numerous premature ventricular contractions occurred. The temperature rose to 100° F. The sinus tract was probed and an abscess cavity was entered 2 inches below the skin surface. The probe then entered a sinus tract 4 inches in length. A small quantity of pus was evacuated. During the remainder of the month the sinus tract was packed, and although the patient was afebrile he continued to complain of right shoulder pain and right lower anterior chest pain aggravated by deep breathing, bowel movements and sneezing. Frequent premature ventricular contractions continued. X-ray of the chest showed a slight irregularity of the right diaphragm not previously noted. The blood count was normal and sedimentation rate 12 mm. per hour.

He was re-admitted to the hospital on November 1, 1953, and the sinus tract was injected with Lipiodol. X-ray examination revealed a cavity in the right upper quadrant measuring 6 cm. in length, lying in the anterior portion of the chest at the level of the lower thoracic spine. The sinus tract was saucerized by the removal of additional cartilage and rib and packed with vaseline gauze. Culture of the tissue removed showed *S. oranienburg* and *Staphylococcus aureus pyogenes*. The immediate postoperative course was complicated by an acute prostatitis, probably induced by catheterization. *Escherichia coli* was cultured from the urine. This infection responded to chloramphenicol, 500 mg. every six hours, streptomycin, .5 gm. every 12 hours, and Crysticillin, 600,000 units twice daily. The *S. oranienburg* organism showed the following order of sensitivity: oxytetracycline, Furadantin, chloramphenicol and Aureomycin, with resistance to streptomycin and bacitracin. The patient was discharged from the hospital November 9, still having a low grade fever, which subsided on November 12. The abscess cavity was irrigated several times daily with chloramine T solution and 0.5% solution of chloramphenicol, but during the following month three cultures were positive for *S. oranienburg*. He returned to work on November 27, afebrile but still complaining of right shoulder pain. Culture from the closing wound was negative for *S. oranienburg* on December 5.

During the major portion of 1954 the patient worked and was in fair health, although still having occasional right shoulder pain and a small sinus tract that would periodically open and close. He was given increasing doses of an autogenous *S. oranienburg* vaccine weekly from February 8 to May 16, 1954, in an effort to increase tissue immunity, although serologic immunity was adequately demonstrated by rapid agglutination of the organism by the patient's serum. During April the sinus tract was curetted and again the culture was positive for *S. oranienburg*. In early September, 1954, pain occurred at the site of the previously resected rib. The end of the rib was very sensitive and painful to pressure. A small sinus tract about 2 cm. distant from the sensitive rib was still draining slightly. The patient was re-admitted to the hospital for the fifth time on September 21. Two and one-half inches of rib and cartilage were removed, the former showing osteomyelitis from which *S. oranienburg* was isolated by culture. The sinus tract was resected as far as the liver, which was exposed and a small portion of infected liver removed. No frank pus was demonstrable. The wound was widely excised and packed with gauze. Microscopic sections showed only shadow forms of hepatic parenchyma in addition to the portal

areas, which were better preserved. There were areas of extensive necrosis involving granulation tissue with abscess formation. Pieces of muscle showed inflammation. Lipogranulomas were found throughout the pieces of dense fibrous tissue. Segments of peripheral nerve were included. Culture showed *S. oranienburg* and *S. albus*, coagulase negative. The salmonella organism showed the following order of sensitivity: Furadantin, Furacin, tetracycline, chloramphenicol, Aureomycin, oxytetracycline, erythromycin and streptomycin. The dry pack was removed September 27 and the patient was discharged afebrile and improved on September 28. The wound was irrigated with Tryptar, and Furacin ointment was applied daily for several weeks. Three cultures taken at bimonthly intervals were negative for salmonella organisms. The wound gradually filled in and closed during the following three months, the right shoulder soreness gradually subsided and the premature ventricular contractions disappeared.

At the present time the patient is well except for considerable postoperative chest deformity and moderate discomfort in the postoperative site, probably the result of paresthesias due to disruption of three intercostal nerves.

Discussion

In a review of the literature no case was found in which *S. oranienburg* has resulted in a chronic subphrenic abscess. Although the relationship between the occurrence of an acute attack of enterocolitis in 1940 and the presence of a chronic salmonella subphrenic abscess 11 years later is mere supposition and cannot be proved, correlation seems probable since the occurrence of "cold abscesses" following infection with organisms such as *S. typhosa* is well known. This is also exemplified in the occurrence of cases of chronic osteomyelitis and chondritis due to infection with salmonella organisms. The presence of *S. oranienburg* in a chronic subphrenic abscess occurring 11 years after an attack of enterocolitis is similar to the case report [34] of chronic intrachondral abscess due to *S. paratyphi B* occurring 14 years after an attack of enterocolitis, except for the location of the abscess and the species of the organism. The abscess was located in the right subphrenic anterosuperior space, bounded by the liver to which it was attached and superficially involved, the rib cage, and the diaphragm, which was incorporated as a part of the wall of the abscess. As to the pathogenesis of the infection, it is believed that the original infection was an acute salmonella enterocolitis accompanied by a bacteremia, with seeding of the subphrenic space with organisms. It is possible, but seems less likely, because of the extent of the involvement, that the infection occurred through the liver with the development of a small subcapsular abscess which subsequently ruptured to form a chronic subphrenic abscess.

The onset of symptoms resulting from a subphrenic abscess caused by any microörganism may be sudden or insidious. When the onset is insidious, as in the case under discussion, the symptom complex is subacute and simulates that of an obscure intra-abdominal lesion. At first the symptoms may be those of vague upper abdominal discomfort without distinct localization. Later the patient may complain of pains and aches in the lower thoracic region or in the flank. At times the pain may radiate to the shoulder, aggravated by deep breathing, sneezing, coughing or bowel movement. The symptom complex is usually progressive, and sooner or later frank signs and symptoms of infection become manifest. The diagnosis and localization of the abscess are frequently

suggested by fixation or elevation of the diaphragm, with secondary effusion in the pleural cavity. This was not present in this case and thus made the diagnosis difficult. A point of tenderness is not infrequently present in the intercostal space, and is not only an important diagnostic sign in subphrenic abscess but is also most helpful in determining the place where drainage should be carried out. This sign was present intermittently and for short intervals during the first year of illness in this case, but was not seriously considered in the differential diagnosis. It is not necessary to wait for local fullness and obliteration of the intercostal space before the diagnosis of subphrenic abscess is suggested.

The two attacks of auricular fibrillation prior to the onset of illness and the frequent premature ventricular contractions during the course of illness seem to have been related to activity of the abscess and were probably produced by a reflex mechanism. It was noted that the premature ventricular contractions became less frequent or disappeared completely each time tension in the abscess was relieved by drainage. The occurrence of cardiac arrhythmias secondary to gall-bladder disease and other disorders below the diaphragm is well known.

The marked relief of pain following cortisone was probably related to the decrease in edema in the region of the abscess, with lessening tension within the abscess cavity.

The surgical approach to a subphrenic abscess must of necessity be considered individually in each case, and will depend upon the location of the abscess.[35] Drainage should be instituted where the abscess is most superficial in relationship to the chest wall. In this case the diagnosis of subphrenic abscess was not established preoperatively. As a result, the approach was made through the abdomen and drainage was therefore inadequate. If the abscess is contiguous with the lower rib cage, as it was in this case, the approach should be through the lower ribs, with resection of ribs and cartilage to insure adequate drainage. Since the abscess was chronic and had a markedly thickened wall containing multiple microscopic abscesses, it becomes evident why drainage and packing of the abscess cavity in an effort to heal the abscess cavity from below were difficult. Three additional surgical excisions of the residual infected tissue and sinus tracts were necessary following the first exploratory operation. The last surgical procedure was done because of the development of osteomyelitis at the end of the previously resected rib.

Although the *S. oranienburg* organism was sensitive in vitro to the antibiotics oxytetracycline and chloramphenicol, there appeared to be little if any therapeutic response of the infection to this mode of therapy. Final cure depended upon adequate excision and drainage of the infected tissue.

Summary

An unusual case of chronic subphrenic abscess due to *S. oranienburg* with contiguous liver infection is reported. Following operation this was complicated by chronic osteomyelitis of the end of a resected rib. In a review of the literature no previous case was found in which *S. oranienburg* produced a chronic subphrenic abscess. It is believed that the subphrenic abscess had its inception 11 years prior to the onset of symptoms, following an attack of acute enterocolitis. When the pathogenesis of the clinical picture is reconstructed

it is presumed that the original infection was an acute salmonella enterocolitis accompanied by a bacteremia, with seeding of the subphrenic space with organisms, or that the infection occurred through the liver, with development of a small subcapsular abscess which subsequently ruptured to form a chronic subphrenic abscess.

The occurrence of reflex cardiac arrhythmias related to activity of the abscess and relieved by drainage is noted. The disturbances of rhythm included frequent premature ventricular contractions and two attacks of auricular fibrillation.

The difficulties in diagnosis and the problems of surgical drainage in cases of chronic subphrenic abscess are stressed. The failure of oxytetracycline and chloramphenicol therapy, in spite of the apparent in vitro sensitivity of the organism to these antibiotics, is evident, and the importance of adequate surgical drainage in the presence of pus is again demonstrated. Four surgical procedures, including excision of infected tissue and sinus tracts, were necessary over a period of approximately two years before cure was effected.

SUMMARIO IN INTERLINGUA

Es reportate un caso inusual de abscesso subphrenic chronic, causate per *Salmonella oranienburg*, con contigue infection hepatic. Post le operation le situation esseva complicate per chronic osteomyelitis del extremitate de un costa resecate. Un revista del litteratura revelava nulle previe caso in que *S. oranienburg* produceva un chronic abscesso subphrenic. Il pare justificate creder que le abscesso subphrenic habeva su inception 11 annos ante le declaration del symptomas, post un attacco de enterocolitis acute. Super le base de un reconstruction del pathogenese del situation clinic on pote supponer que le infection original esseva un acute enterocolitis a salmonella accompaniate de bacteremia e resultante in un dissemination del organismos in le spatio subphrenic. Il es etiam possibile que le infection occurreva via le hepate, con le disveloppamento de un parve abscesso subcapsular que se rumpeva subsequentemente e formava assi un abscesso subphrenic chronic.

Es signalate le occurrentia de reflexe arrhythmias cardiac in relation al activitate del abscesso e alleviabile per drainage. Le disturbationes del rhythmo includeva le frequente occurrentia de prematur contractiones ventricular e duo attaccos de fibrillation auricular.

Es sublineate le difficultates diagnostic e le problemas del drainage chirurgic in casos de abscessos subphrenic chronic. Therapia a oxytetracyclina e chloramphenicol es sin effecto in despecto del sensibilitate del organismo a ille substantias in vitro. Le importantia de un adequate drainage chirurgic in le presentia de pus es demonstrate de novo. Quatro manovras chirurgic, incluse le excision del histos inficite e del tractos sinusal, esseva necessari pro effectuar le curation al fin de un periodo de circa duo annos.

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OCHRONOSIS: REPORT OF A CASE*

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Ochronosis is an extremely rare disorder but, when present, is quite disabling. We have recently had an opportunity to observe a patient with alkaptonuria and secondary ochronosis. It has been noted that alkaptonuria may be present for many years before the signs and symptoms of ochronosis become pronounced. If alkaptonuria is detected early, the onset of the so-called alkaptonuric or ochronotic osteoarthritis may perhaps be delayed.

In 1866 Virchow recorded the first case of ochronosis, describing the pigmentation of cartilage and other tissues. More than 200 cases of alkaptonuria and 100 cases of ochronosis have since been reported. Several groups of workers have reviewed the literature and added the clinical as well as the metabolic observations.[1-6]

The following case meets the criteria of ochronosis.

Case Report

The patient, a 38 year old cook, complained of fatigue and pain in his back of 11 years' duration. For the last two years he had noted that his urine turned black on standing. There was no family history of backache or melanuria.

In 1944 he experienced stiffness in the lumbar area of the back and pain in the left shoulder. The stiffness appeared in the morning with initial movements in practically all of the body joints. During 1945 while in the Army he sustained partial deafness from a bombardment. In May, 1946, he was hospitalized for a deep phlebitis in his left leg, which was treated surgically by ligation of the left femoral vein. Roentgenologic investigation of his spine at that time revealed a slight irregularity involving the superior-anterior margins of the first lumbar vertebra. Some flattening of the lumbar curve and minimal narrowing of the lumbosacral joint were noted. Laboratory studies were within normal limits. His weight was recorded as 170 pounds and his height as 65½ inches. The general physical examination was reported to be within normal limits.

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In December, 1949, he was hospitalized again because of pain in the back and left shoulder, and episodes of peripheral joint swellings, which had occurred intermittently since 1944. The results of the physical examination revealed partial deafness and impaired mobility of the vertebral column, with tenderness over the sacro-iliac area. The remainder of the physical examination and the laboratory studies were within normal limits. A roentgenogram of the left shoulder revealed an osteochondral body in the acromioclavicular articulation. Roentgenograms of the spine demonstrated a posterior luxation of the twelfth dorsal vertebra on the first lumbar vertebra, with marked narrowing of the interspace. There was subchondral sclerosis of the adjacent articulating margins. Phantom nuclei, representing complete loss of nuclear substance, were noted in the region of the intervertebral discs.

In October, 1952, the patient was again hospitalized because of severe backache of two weeks' duration. He noted needle-like pain extending down both arms to his hands, with numbness of his hands. He continued to complain of fatigue. The physical examination revealed restriction of the lower back motion and limited chest expansion. Laboratory studies were normal. Roentgenograms of the spine revealed that practically all the disc spaces, from the mid-dorsal region to the sacrum, were diminished, with calcification. The sacro-iliacs were normal. The orthopedist who examined the patient concluded that some type of spondylitis was present, possibly a primary fibrous type of disease. The arthritis consultant did not consider this to be rheumatoid arthritis but a condition secondary to a process in the intervertebral discs. It was his opinion that the patient had a disease process of unknown origin, producing atrophy of the intervertebral discs. It was at this time that the patient was told he had diabetes mellitus.

In 1953 the patient saw his local physician because his urine turned black a few hours after micturition, and because his shorts and the axillary portion of his undershirts were stained black. He was told he had alkaptonuria.

In March, 1955, the patient came to the Lahey Clinic with the chief complaints of backache, which had increased since 1944, and melanuria of two years' duration. The physical examination revealed the following positive findings: weight, 160½ pounds, and height, 63¼ inches, as compared to 170 pounds and 65½ inches in 1944; mild obesity; discoloration of the cartilage of the right ear; area of discoloration of the cornea of the left eye, and superficial varicosities. The gait was normal and the spine straight, with no pelvic tilt. There was difficulty in moving about; he did not flex the spine on rising but pushed himself up from the table with his hands. No tenderness was noted. Shoulders, hips, elbows and knees were normal.

Laboratory examinations revealed the following abnormal findings: the specific gravity of the urine was 1.006, and there was a trace of sugar. Alkapton bodies were present. The urine turned black when sodium hydroxide was added to it immediately after micturition. A black precipitate was noted when silver nitrate solution was added to the urine.

Roentgenologic studies revealed that the chest, knees, ankles, hands and elbows were normal. Films of the left shoulder demonstrated an abnormal calcification adjacent to the acromioclavicular junction. Films of the cervical spine showed a reversal of the curvature, with degenerative marginal changes. Films of the dorsal and lumbar spine revealed a narrowing of all of the discs and sclerotic changes on the opposing surfaces of the adjacent vertebrae, with disc calcification and minimal hypertrophic changes (figure 1).

In cases of ochronosis the discs are narrowed, with calcification in the annulus fibrosus and secondary osteoarthritic changes of several dorsal and lumbar spinous processes.

FIG. 1. Note sclerotic changes on opposing surfaces of adjacent vertebrae, with calcification of the discs and minimal hypertrophic changes.

Comment

We have presented a case of alkaptonuria with secondary ochronosis in which symptoms had been present for at least 10 years. Because of his occupation as a chef, this patient had been eating a diet containing excessive amounts of protein. The characteristic features of ochronosis had been present for a long time; they included (1) dark staining of underclothing from urine and perspiration; (2) diabetes mellitus which had been diagnosed in the past; (3) bluish discoloration of cartilages of the ears and pigmentation of the sclerae; (4) presence of urinary homogentisic acid, and (5) typical roentgenologic findings.

This patient has been treated with high doses of ascorbic acid (1,000 mg. daily), a low protein diet, acetylsalicylic acid in doses adequate to insure comfort (10 to 50 gr. daily), heat in the form of hot tub baths, heating pads and hydrocollator steam packs. Extra rest periods and elimination of unnecessary weight bearing were also advised. On this program he has experienced a sense of well being and a general reduction of all previous symptoms. Also, the darkening of the urine by the addition of sodium hydroxide solution was delayed from an immediate reaction to three to four hours.

It cannot be determined at this time which portion of the above program was directly responsible for the patient's improvement.

Summary

A case of ochronosis has been presented with the complete triad of homogentisuria, pigmentation of the sclerae and of the cartilages of the ear, ochronotic arthritis and spondylitis.

Summario in Interlingua

Ochronosis pote esser invalidante. Usualmente le presentia de pronunciate signos e symptomas de ochronosis es precedite per multe annos de alcaptonuria. Le prompte detection de alcaptonuria rende possibile le application de mesuras capace a retardar le declaration del si-appellate osteoarthritis alcaptonuric o ochronotic.

Es reportate le caso de un cocinero de 38 annos de etate qui habeva habite symptomas durante 11 annos. Durante le passate duo annos su urina habeva disveloppate un coloration nigre post remanentia in vitro. Le typic aspectos de ochronosis habeva essite presente durante un longe tempore. Illos includeva (1) coloration fuscate del subvestimentos per urina e transpiration, (2) diabete mellite, que habeva essite diagnosticate in le passato, (3) discoloration blauastre del cartilagines del aures e pigmento del scleras, (4) presentia de acido homogentisic in le urina, e (5) typic constatationes roentgenologic.

Iste patiente ha essite tractate con alte doses de acido ascorbic (1.000 mg per die), un dieta a basse contento de proteina, acido acetylsalicylic in doses adequate a assecurar un sensation de ben-esser (10 a 50 granos per die), e calor in le forma de banios calide, cossinos calefactive, e compressas a vapor. Esseva etiam recommendate periodos additional de reposo e le elimination de omne non inevitabile portar de objectos pesante. Iste programma ha resultate pro le patiente in un sensation de ben-esser e le reduction de omne previe symptomas.

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PRIMARY MENINGOCOCCAL LOBAR PNEUMONIA WITHOUT MENINGITIS *

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Except for a brief period after World War I, meningococcal pneumonia occurring in the absence of meningitis has rarely been described. In 1919 several studies were made of postinfluenzal pneumonia. Holm and Davison [1a and 1b] reported 403 bacterial pneumonias following influenza in 1,510 patients. There were 85 instances of meningococcus grown from the sputum. The clinical courses of 23 who came to post mortem were summarized. The onset was acute, with chill followed by cough, often with pleuritic pain, high temperature (103 to 106° F.), prostration and cyanosis. The physical signs were those of lobar pneumonia or bronchopneumonia. Culture of the lungs was said to have been "pure" in seven and "mixed" in 16, but no tabulation of the other bacteria recovered was made. Meningitis occurred in 22 of the 85 with positive sputa. Essentially the same experience was recorded by Kinnicutt and Binger,[2] Meader, Means and Hopkins [3] and Fletcher.[4]

No particular reference was made to the disease from that time until 1944, when Potter, Reid and Bronstein [5] described 11 patients with meningococcemia without meningitis. Their case 11 had a clinical picture suggesting pneumonia, but this was not documented with culture or satisfactory roentgen study. Four years later Brick [6] reported two patients with meningococcal pneumonia without meningitis. These cases occurred in 1942. One patient (P. C.), treated with sulfadiazine, was found to have a nontypable meningococcus in the blood; this was not detected in the sputum. He had no skin rash. The other patient (L. L.) grew a type I meningococcus from the sputum and pleural fluid, and a type XV pneumococcus from the sputum only. He had a petechial eruption

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on the lower extremities. In 1945 Roberg [7] reported a severe pneumonia occurring in an 18 year old soldier. The sputum was described as creamy and abundant. Cultures grew out 75% meningococci and 25% beta hemolytic streptococcus. This patient had a morbilliform—but not a purpuric—eruption, and recovered on sulfadiazine after a stormy course. These three are the only documented instances of meningococcal pneumonia in the absence of meningitis in the recent past. Hoyne and Brown [8] and Daniels [9] comment on pneumonia as an occasional complication of meningitis, and both associate it with a poor prognosis. Its bacteriology is not discussed.

Case Report

A 64 year old tailor entered the Presbyterian Hospital for the third time because of a shaking chill, pleurisy and stupor of 12 hours' duration.

He had first been seen in September, 1951, at which time he underwent subtotal gastrectomy, duodenectomy, pancreatectomy and splenectomy for separate carcinomas of the gastric antrum and the ampulla of Vater. Postoperatively he developed diabetes mellitus and a pancreatitic deficiency-malabsorption syndrome, but was managed well with diet, insulin and enzyme replacement therapy. At the time of a routine clinic visit on November 2, 1953, 26 months after a histologically complete resection of his tumors, a rectal shelf was palpated. However, he felt very well. His weight was maintained at 135 pounds, and he worked regularly as a tailor. Clinically, radiologically and from the laboratory standpoint there was no other evidence of metastasis.

On November 18, 1953, he entered the Presbyterian Hospital in a state of shock. An upper respiratory infection had lingered for two weeks but was mild enough to allow him to work until the day prior to admission. That night he experienced a single shaking chill, followed by a temperature rise to 103° F. Subsequently he developed a nonproductive cough and left-sided pleurisy. When he became stuporous his family thought he was in insulin shock. When oral sugar did not arouse him he was brought to the hospital, 12 hours after the onset of his chill.

Physical examination revealed a barely detectable blood pressure of 60/40 mm. of Hg, a pulse of 120 palpable only in the femoral vessels, respirations of 30 per minute, and a temperature of 103° F. He was stuporous but not comatose. His skin, lips and nail-beds were blue-gray and the extremities were cold. There was no edema, no skin rash or petechiae and no nuchal rigidity. The fundi were normal. Auscultation of the lungs revealed only decreased breath sounds and a few rhonchi at the left base posteriorly, with splinting. The heart sounds were inaudible. Abdominal palpation was negative. There was no neurologic defect.

The significant initial laboratory data were an erythrocytic sedimentation rate of 14 mm. in one hour, a hemoglobin of 13.2 gm./100 ml., and a white cell count of 6,200, with 68% neutrophils, only 4% of which were segmented. In the bladder there were only 20 ml. of urine, with specific gravity of 1.022, 1 plus proteinuria, and no cells or casts. The blood sugar was 180 mg./100 ml., and the nonprotein nitrogen was 51 mg./100 ml. An electrocardiogram was normal. Chest x-ray showed a homogeneous density in the left lower lobe.

The patient was thought to have a bacterial pneumonia with septicemia and peripheral circulatory collapse. After appropriate cultures were taken, intramuscular penicillin and intravenous Terramycin were begun. A continuous intravenous drip of Levophed was used to maintain systolic blood pressure in the 100 mm. of mercury range. His diabetes was controlled with standard insulin according to urine test.

Temperature dropped promptly to below 100° F. by the second day. At that time signs of consolidation were present at the left base. The leukocyte count rose to 17,000 and then to a maximum of 24,000 on the fourth day. He responded well to antihypotensive measures and regained full consciousness, warmth and urine flow in six hours, but it was necessary to continue Levophed for just over two days.

Bacteriologic data revealed that the peritoneal exudate from a mouse injected with sputum contained a type 32 pneumococcus. The sputum plate, on the other hand, was overgrown with large colonies of meningococci, and no pneumococci were detected. The blood culture also contained meningococci. The microörganism fermented dextrose and maltose but not sucrose, and was agglutinated to titer with type 2A antimeningococcal serum.

After the diagnosis was established the patient was treated with penicillin alone for a four-week period, during which time serial x-rays showed gradual resolution, never complete. There was a prolonged convalescence. His subsequent course in the hospital was not otherwise remarkable.

In the fifth week an ACTH test showed normally functioning adrenal glands. Although there was nothing in the history to suggest a prior specific infection, acute and convalescent sera were tested for antibodies to influenza A, A′ and B, Q-fever, psittacosis and lymphocytic choriomeningitis. There were no significant increases in titer to any of these agents.

One year later the patient returned to the hospital. In the interval he had been relatively well. During this admission he died in uremia because of bilateral ureteral block from his metastatic carcinoma. Postmortem examination revealed tumor infiltration through the diaphragms into the lung bases. The adrenal glands were normal.

Discussion

Meningococcal lobar pneumonia is a rare disease and has been documented only four times since the postinfluenzal epidemics of World War I. Since the meningococcus may occur as the etiologic agent together with a pneumococcus, some of the infections can be overlooked if mouse inoculation is the only isolation technic used. A purpuric rash, usually the striking clinical sign of meningococcemia, may be absent. At least, it was not found in three out of four cases herein reviewed.

The clinical picture in our patient did not differ from that seen in a maximally severe pneumococcal pneumonia, and treatment was also the same. Both organisms, of course, are very sensitive to penicillin. The importance of recognizing the bacterial cause of meningococcal pneumonia is that it constitutes an indication for administering prophylactic sulfadiazine to familial and hospital contacts.

The peripheral circulatory collapse in our patient was presumably related to the meningococcemia, but it is not a specific finding. It responded to Levophed treatment alone.

Summario in Interlingua

Post le prime Guerra Mundial, pneumonia meningococcal sin meningitis esseva notate e describite per plure autores como sequela sporadic de influenza pandemic. Tamen, durante le passate 35 annos le litteratura medical—in tanto que nos ha potite examinar lo—presentava solmente tres casos a documentation adequate. Le evidente raritate del condition induce nos a reportar le occurrentia de un caso tractate in novembre 1953 al Hospital Presbyterian del Citate de New York.

Nostre patiente esseva un sartor de 51 annos de etate qui, duo annos retro, habeva essite subjicite a gastrectomia subtotal, duodenectomia, pancreatectomia, e splenectomia pro carcinoma. Ben que ille disveloppava diabete e carentia pancreatic post le operation, su symptomass esseva neutralisate per appropriate therapias de reimplaciamento. Durante duo septimanas ille habeva habite un leve infection supero-respiratori. Postea, 12 horas ante su admission al hospital, ille habeva algor febril, sequite per tusse, febre, dolor sinistro-thoracic, e finalmente stupor. Al tempore de su admission ille esseva in choc, con cyanosis blau-gris, quasi imperceptibile pulso e pression sanguinee, e inaudibile sonos cardiac. Le examine roentgenologic revelava consolidation del lobo sinistro-inferior. Le pelle monstrava ni eruption ni petechias. Le collo non esseva rigide.

Post le obtention del appropriate materiales de culturation, le patiente esseva tractate con massive doses de penicillina intramuscular, Terramycina intravenose, e un continue inguttation intravenose de Levophed. Iste therapia resultava in un reprisa Le temperatura se abassava, e le patiente redeveniva consciente. Pro mantener le pression de sanguine, Levophed esseva requirite durante 48 horas.

Culturas de sanguine effectuava un crescentia de meningococco, typo 2A. Un cultura de sputo etiam effectuava un crescentia de meningococco, apparentemente in forma pur. Tamen, pneumococco typo 32 esseva obtenite ab muses post injectiones intraperitoneal de specimens de sputo.

Post que le diagnose bacteriologic esseva establite, le therapia esseva restringite a penicillina e continuate durante un periodo total de quatro septimanas. Le convalescentia esseva lente sed ultimemente complete. Un anno plus tarde le patiente retornava al hospital e moriva ab recurrente carcinoma metastatic.

Isto pare esser un indubitabile caso de pneumonia lobar meningococcal sin meningitis. Le importantia del recognition de iste raritate es que su occurrentia es un indication que doses prophylactic de sulfadiazina debe esser administrate al membros del familia del patiente e a su contactos al hospital.

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EDITORIAL

THE RELATION OF CIGARETTE SMOKING TO BRONCHOGENIC CARCINOMA

THE rapidly accelerating death rate from bronchogenic carcinoma during the last several decades has naturally aroused keen interest and stimulated many investigations, largely centered on the rôle smoking may play in the increase. An extensive literature has accumulated, including many statistical studies which may be confusing to some readers, not so much because of variation in the facts reported as because of contradictory conclusions, sometimes expressed with much heat and even rancor. The question is still open, especially as to interpretation, but it should be possible now to reach at least tentative conclusions of some practical value.

How great is the increase? Is it real and not merely a result of improved diagnosis? That the increase in the number of cases recognized is huge is indicated by clinical investigations, vital statistics and autopsy records. In the United States the reported death rate per 100,000 rose from 2.7 in 1930 to 11 in 1948,[1] and the total number of deaths reported from 3,000 in 1930 to 23,000 in 1953.[2] Cancer of the lung now causes more deaths in males than any other cancer or (in California) than tuberculosis.[1] It is reported to cause 4% of all deaths in males between 45 and 64.[1, 3] In Britain, Doll [3] reported an increase in recorded deaths per million (crude rates) from eight in 1900 to 20 in 1920 and 321 in 1952. Reports from practically all other countries with adequate records, including Turkey and Japan,[4] show a similar trend, although varying considerably in the degree of increase and the time at which it became notable.

Undoubtedly improved diagnostic methods have contributed to this increase in rates. It is impossible at present to measure this effect precisely, but it appears to be a minor factor. The rise has been marked in teaching hospitals with a high percentage of autopsies as well as in the general population.[3, 4] It is as marked in country areas as in the cities.[4] The rate of increase in males has been at least two and one-half times as great as in females,[3, 5] who had the same ready access to all available diagnostic facilities. Furthermore, the acceleration of the rate is continuing, although

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there is no corresponding continuing improvement in the diagnostic measures.

If this increase must be accepted, how can it be explained? What is really known about the causes or even the precipitating factors of cancer in general or bronchial cancer in particular? Obviously there must be an underlying individual susceptibility—the soil must be fertile. Of all subjects exposed to any of the suggested carcinogenic agents, only a few develop the disease. Concerning the nature and cause of such susceptibility nothing is really known, and at present nothing can be done about it.

The gross increase during the last half-century may reasonably be attributed to some specific carcinogenic agent or agents, not necessarily chemically identified, presumably active on inhalation. Such substances must have been introduced in significant amounts at about the beginning of this century and have been present in increasing concentrations since. Search for such an agent has been largely directed along three lines. First, specific occupations involving exposure to certain dusts and fumes. Second, more general atmospheric pollution, especially with smoke from coal and oil furnaces, and exhausts from gasoline and Diesel engines. Third, tobacco smoke, especially cigarette smoke.

There is little doubt as to the carcinogenic effect of certain of these occupational exposures, after long latent periods of 10 to 20 years or more, particularly in miners of radioactive ores and in workers with chromates, asbestos and quite possibly with arsenic, nickel and beryllium.[6] Coal dust itself seems not to be carcinogenic, but active carcinogenic substances have been demonstrated in the tars and oils derived from the destructive distillation of coal. A similar action seems to be exerted by the mists of lubricating oils and by certain metallic dusts and fumes, such as those to which welders are exposed.[6] There is as yet no direct conclusive evidence that these latter exposures cause many human cases of lung cancer, and in any event only limited groups would be involved. Such occupational exposures can explain only a small fraction of lung cancers.

The second and third lines of investigation offer much more promise. Extracts carcinogenic for mice when painted on the skin during about half the life span of the animal, containing one known carcinogen, benzpyrene, in minute amounts, have been obtained from cigarette smoke,[7] from the exhaust of gasoline engines, particularly if operating inefficiently, from soot and smoke arising from the incomplete combustion of coal and oil, and from filtrates of the atmosphere when heavily polluted with these substances.[8, 9]

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[8] Kotin, P.: The rôle of atmospheric pollution in the pathogenesis of pulmonary cancer, Cancer Research **16**: 375–393, 1956.

[9] Stocks, P., and Campbell, J. M.: Lung cancer death rates among nonsmokers and pipe and cigarette smokers, Brit. M. J. **2**: 923–929, 1955.

Both cigarette smoke and air so polluted have been blamed for the recent increase in bronchogenic carcinoma; theoretically, either or both could be concerned, and many of the investigators are sharply divided in their opinions, some enthusiastically and even heatedly supporting one view to the virtual exclusion of the other. Occasionally, perhaps, wishful thinking has distorted judgment. More often, this divergence probably stems from the different standpoints of the statistician who demands precise mathematical accuracy, and the physician who, if he is to treat patients, must customarily attempt to draw conclusions and take decisive action on the basis of information which is neither precise nor adequate in the strict sense, and who may be thankful to get "evidence so strong as to be considered proof within the everyday meaning of the word." [10] The problem is manifestly important and urgent from the standpoint of public health as well as for the individual smoker, as bronchogenic carcinoma is becoming a major risk for males over 50. Are there facts available which warrant some tentative conclusion as to the part smoking probably may play? Limitations of space preclude more than a brief summary of the major features of the problem, with citation of a few representative studies.

If we disregard many suggestions of an association of smoking with lung cancer, based largely on personal impressions, perhaps the first serious study is that of Müller,[11] who investigated the smoking habits of 86 patients with carcinoma of the lung and those of 86 control subjects. He reported that 50% of the cancer cases were heavy smokers, and 3.5% nonsmokers, whereas 10% of the controls were heavy smokers and 16.3% abstainers. His technical methods do not withstand the criticism of professional statisticians, but the results do conform in general to those of subsequent similar studies.

One of the best investigations of this type is that of Doll et al.,[4, 12] in Great Britain. They assembled a group of 2,710 cases of cancer, including 1,465 cases of pulmonary cancer, and 1,632 controls, from a group of London and provincial hospitals. As soon as feasible after notification that a patient with known or suspected cancer had been admitted, the subject was interviewed by one of four instructed lay "almoners," using a detailed questionnaire, with special reference to the type, duration and quantity of smoking and to occupation and possible industrial exposures. For each case of lung cancer a control case was selected, of the same race, sex and age (by decades), and in the same hospital at the same time, but at random in all other respects. A tabulation showed fewer nonsmokers (who had never habitually smoked as much as one cigarette per day for one year), and more heavy smokers (more than 25 cigarettes per day for many years)

[10] Editorial: Cancer of the lung, New England J. Med. **249**: 465–466, 1953.
[11] Müller, F. H.: Tabakmissbrauch und Lungencarcinom, Ztschr. f. Krebsforsch. **48**: 57–85, 1939.
[12] Doll, R., and Hill, A. B.: A study of the aetiology of carcinoma of the lung, Brit. M. J. **2**: 1271–1286, 1952.

in the cancer groups, for males and females, than in the controls. Thus nonsmokers in males numbered 0.5% of the cancer group and 4.5% of the controls, and heavy smokers 25% and 13.4%, respectively. These figures are statistically significant.

As illustrative of similar studies in this country, we may refer to the report of Wynder and Graham,[5] who studied similarly 605 cases of pulmonary carcinoma (in males) and 780 carefully selected controls. There were 1.3% of nonsmokers in the cancer group, and 14.6% in the controls. Moderate to chain smokers comprised 86.4% in the cancer group and 54.7% of the controls, while excessive to chain smokers numbered 51.2% and 19.1%, respectively. These figures are highly significant.

Sadowsky et al.[13] have reported a similar study of 2,605 white males, a "representative sample," of patients coming into hospitals in New York, Chicago, Missouri and New Orleans. These were questioned by four lay interviewers as to their smoking habits. The series included 472 cases of pulmonary cancer and 592 suitable controls. The frequency of pulmonary cancer was, without exception, higher in all the groups in smokers of cigarettes alone or in combination with pipe or cigars, from 3.7 to 6.6 times that in nonsmokers. Cutler [2] has reviewed and summarized 14 important retrospective studies of this type which agree in showing the same trend, although there is considerable difference between the actual figures in some of the studies. These figures apply to the common types of bronchogenic carcinoma, the epidermoid (squamous) and undifferentiated cell types. There is very little evidence of an association of smoking with the rarer adenocarcinoma, which for unknown reasons is relatively common in females.

The figures reported above are "statistically significant," in many cases highly so, and in aggregate they seem to prove a definite association between the practice and the degree of smoking (cigarettes) and the frequency of pulmonary cancer. Obviously such an association is real or "meaningful" only if the data on which the figures are based are accurate. Retrospective studies of this type have been severely criticized by statisticians [14, 15] because of bias, both in the questioning as to smoking habits and in the selection of the subjects. In most cases the questioners knew or sensed the situation and, without intending to distort, may have favored the association they were investigating. There is intrinsic evidence in several of the larger series that such bias was avoided. Thus, in Doll's series [4] 14% of the cases initially diagnosed as cancer of the lung (at the time of questioning) later were proved to have some other malady. Their smoking habits, however,

[13] Sadowsky, D. A., Gilliam, A. G., and Cornfield, J.: Statistical association between smoking and carcinoma of the lung, J. Nat. Cancer Inst. **13**: 1237–1258, 1952–1953.

[14] Berkson, J.: The statistical study of association between smoking and lung cancer, Proc. Staff Meet., Mayo Clin. **30**: 319–343, 1955.

[15] Arkin, M. H.: Relationship between human smoking habits and death rates. An analysis of the American Cancer Society Survey, Current M. Digest **22**: 37–44 (Apr.) 1955.

corresponded to those of the control group and not to those of the cancer group. The same was reported in 19% of the cases in Levin's series.[16, 2] Of Wynder and Graham's cases,[5] 286 had not been diagnosed at the time of the interview. Of these, 100 later proved to have carcinoma and 186 some other malady. The smoking habits of these subjects corresponded to those of the appropriate group. It seems very probable, therefore, that this type of bias did not distort the results to any disturbing degree.

There is more doubt as to the proper selection of the groups. In most studies of this type, cancer cases have been assembled from one or more hospitals, taking all appropriate cases entering consecutively until the requisite number had been secured. The controls have usually been taken from noncancer cases, occasionally cancer at other sites, entering the same hospital at about the same time, more or less carefully matched as to age, etc. The latter group is especially vulnerable to criticism, but in Doll's series and in at least several of the American studies they seem to have been selected with great care. As many have pointed out, such "segments" cannot be regarded as "strictly and truly representative of the general population." This is not really essential, however, if the controls and the cases of cancer come from the *same* population,[2] and this seems to have been secured in the better studies. In a few investigations, e.g., Wynder and Cornfield's study in physicians,[17] in which nonhospitalized groups were utilized, similar results were obtained. It seems doubtful whether the better of these studies could be materially improved, or whether conviction could be secured by their indefinite repetition.

Bias in the interviews, and some but not all of the other objections,[18] can be avoided in prospective studies in which the smoking habits are determined in a large number of individuals selected from the general population, and observed for three to five years for the appearance of carcinoma or any other disease under study. Thus Doll [19] distributed questionnaires regarding smoking habits to 59,000 registered physicians in Great Britain and, after discarding females and males under 35, secured 25,000 usable records. In a follow-up 29 months later, 789 deaths were reported, including 35 cases of pulmonary cancer. In these 35 cases (as well as in deaths from coronary thrombosis) the rate per 1,000 increased as the amount of smoking increased, quite in harmony with his retrospective studies. The numbers are still small but the agreement is good.

In the United States Hammond and Horn [20] have reported preliminary observations of an extensive prospective study carried out under the auspices

[16] Levin, M. L. et al.: Cancer and tobacco smoking, J. A. M. A. **143**: 336–338, 1950.

[17] Wynder, E. L., and Cornfield, J.: Cancer of the lung in physicians, New England J. Med. **248**: 441–444, 1953.

[18] Mainland, D. et al.: The risk of biased selection in forward-going surveys with nonprofessional interviewers, J. Chron. Dis. **4**: 245–252, 1956.

[19] Doll, R., and Hill, A. B.: The mortality of doctors in relation to their smoking habits, Brit. M. J. **1**: 1450–1455, 1954.

[20] Hammond, E. C., and Horn, D.: The relationship between human smoking habits and death rates, J. A. M. A. **155**: 1316–1328, 1954.

of the American Cancer Society in 1952–1953. They obtained usable questionnaires regarding smoking habits from 190,134 white males between 50 and 69 years of age. Of these, 187,766 were traced through October 31, 1953, by which time 4,854 had died. Their figures indicated a higher death rate from lung cancer (three to nine times greater) at all ages among smokers, particularly cigarette smokers, than in men who had never smoked regularly, and lung cancer was five to 16 times more common among men smoking a pack or more per day. They found deaths from all causes about 50% higher in smokers than in nonsmokers. About half of this excess was attributed to coronary arterial disease and about a quarter to cancer, largely lung cancer. The death rate from cancer in other locations, however, was also somewhat higher in smokers. (Some critics claim that they "have proved too much.") "Another year or two of follow-up must precede estimation of the degree of the effect with more precision."

The figures and conclusions of Hammond and Horn have been severely criticized by statisticians,[14, 15] particularly on the ground that the subjects were improperly selected and do not constitute a typical segment of the general population. They were selected by 22,000 lay volunteer workers in 394 counties in nine states—three Eastern and five Middle Western states, and California. Each included metropolitan, smaller urban and rural areas. Each volunteer was instructed to submit a questionnaire to 10 or more white males of from 50 to 69 years of age, selecting such as would presumably be available for follow-up studies for several years. This obviously introduces one form of selection, by eliminating all who were acutely or chronically ill. This is evident in their results, which show death rates significantly lower than the average for the United States as a whole. This type of selection, provided it favored neither group—the smokers or the nonsmokers—appreciably, need not affect the validity of the results significantly if the period of follow-up were long enough. The experience of life insurance companies indicates that the effects of selection of risks for ordinary policies on the basis of their questionnaires and physical examinations are largely dissipated after five years. Since some selection is evident, it seems prudent to await a later follow-up before attempting to decide as to the precise validity of their figures. Even though there is no firm assurance that the selection was not biased in other respects, it would be surprising if the trend indicated in the preliminary study was not confirmed.

It has been reported [2] that another large prospective study has been undertaken by the National Cancer Institute and the Veterans Administration, based on questionnaires from 220,000 veterans holding life insurance policies issued by the government. The results of this study, when available, should furnish more dependable data, since adequate follow-ups are assured and personal bias in selection of subjects seems excluded.

To meet the criteria of statisticians for strict mathematical precision, suitably planned experiments have been suggested, obviously a ridiculous im-

possibility with human subjects. We must take our smokers as we find them. The substitution of animals in such experiments seems equally futile, for there is no adequate reason to expect that breathing air in a room or cage tainted with tobacco smoke is equivalent to smoking and inhaling, or that it will cause cancer in man or in mice.

The best substitute seems to be a prospective study over widely distributed areas in which subjects are chosen by a completely "random" process of selection. To secure a requisite number of cases of cancer within a reasonable time, a far larger group would be required. The cost of selecting many thousands of subjects in this way and following them up adequately for at least three to five years would be staggering. No single feasible study will give a conclusive answer to this question. The subject is too important, however, to abandon because perfection cannot be attained. Investigations must be carried out from many lines of approach and an attempt made to reach some reasonable conclusions with the data and means that are available. The recent report of Haenszel and Shimkin [21] is encouraging in this respect. Their analytic study indicates that the excess risk of lung cancer among smokers demonstrated in special groups also applies to the general population. The correspondence was "good," and their results did not contraindicate such a generalization.

Assuming that these figures deserve any credence, the carcinogenic effect of smoking seems largely restricted to cigarette smokers, "pure" or "mixed." The failure to show any clear association of pure cigar or pipe smoking with pulmonary cancer (although there is with cancer of the lip) has been advanced as an objection to the tobacco theory. Objection has also been raised because no clearcut relation to inhalation has been demonstrated, as in Doll's studies. This is fallacious, since a large majority of pure cigarette smokers do inhale significantly, unconsciously if not deliberately.[5] This may not be true of mixed smokers, and a majority of cigar smokers do not inhale habitually. This difference in manner of smoking might offer a reasonable explanation for the apparent difference in carcinogenic effect, although the point has not been proved.

There is usually a good linear relationship with the amount of smoking, a lower incidence in those smoking less than 10, and much higher in those smoking over 20 cigarettes a day. The increased incidence of carcinoma of the lung does not usually become notable until after a protracted period of such smoking, at least 10 and usually 20 to 30 years. In Wynder and Graham's series,[5] 96% of the cases of pulmonary cancer had smoked for over 20 years, 85% for over 30 years, and 50% for over 40 years. This may be in part a matter of aging, but the average age at death of males from lung cancer is lower by about a decade than from most other types,

[21] Haenszel, W., and Shimkin, M. B.: Smoking patterns and epidemiology of lung cancer in the United States. Are they compatible? J. Nat. Cancer Inst. 16: 1417–1441, 1956.

and no other manifestation of early senility has been noted. Such a lag is not unusual, having been observed also, for example, in the miners of radioactive ores.

The objection has been raised that the date of onset of the increase of pulmonary cancer varied greatly in different countries, and that the correlation between these dates and the increased consumption of cigarettes is poor as compared with atmospheric pollution.[6] In view of the long and presumably variable lag in the effects of smoking, such an analysis is difficult and likely to be misleading, although it merits consideration. In Scandinavian countries, for instance, there was a notable lag in the increase of pulmonary cancer as compared with Great Britain and the United States. In Denmark, however, where the rate has become high, Clemmesen [22] has concluded that "there is no reason to assume any carcinogenic influence of atmospheric pollution as far as Denmark is concerned." Also in Great Britain, the incidence of pulmonary cancer in men is considerably higher than in the United States, although the average consumption of tobacco is less. The activity of associated carcinogens has been suspected but not proved. The reason is not obvious, but a precise linear relationship between localities so diverse can scarcely be expected.

There is a higher incidence of pulmonary cancer in urban than in rural areas, both in Great Britain and the United States and in Scandinavian countries, about twice as high in Doll's series. He found also a higher proportion of smokers, especially heavy smokers, in the urban areas. The incidence of cancer in the urban groups was somewhat higher than would be expected from the amount of smoking, and suggested either some additional carcinogen or a change in the relative smoking habits of the groups. In nonsmokers, however, he found no significant difference in the incidence of pulmonary cancer between urban and rural groups.[23]

The marked difference in sex incidence has also been advanced as an objection to the smoking theory. The ratio in the U. S. Department of Health figures for 1953 is given as 5 to 1. Doll reported a ratio in Great Britain of 6 to 1. In limited groups it has been much higher, as in that of Wynder and Graham at the Barnes Hospital, which was 18 to 1. This discrepancy has continued to increase, although smoking among women has increased greatly during the last decade. This increase in smoking, however, has been largely among the girls and younger women, who have not been heavy smokers long enough, presumably, to show any notable carcinogenic effects as yet. But few women in the cancer age have been heavy smokers for any protracted period. If the apparent carcinogenic effect of smoking is real, we may expect to see a leveling off of the rate in males and a rapid increase in females over the next two decades. Careful

[22] Clemmesen, J. et al.: The increase in incidence of carcinoma of the lung in Denmark, Brit. J. Cancer 7: 1–9, 1953.

[23] Doll, R.: Mortality from lung cancer among nonsmokers, Brit. J. Cancer 7: 303–312, 1953.

studies in females, prospective and retrospective, seem to offer the best immediate prospect of providing a definite answer to the problem. A moderate difference in sex incidence might be explained by different degrees of exposure to atmospheric pollution, but the differences observed seem much too great to be explained on that basis. Although a difference in susceptibility of the sexes to such carcinogens has been postulated this is not supported by direct evidence. Doll's studies of nonsmokers [23] showed essentially the same frequency of pulmonary carcinoma in males and females.

In spite of the defects and possible sources of error in these studies, the accumulating evidence points strongly to a definite and "meaningful" association between cigarette smoking and lung cancer. A single study of this type would have little significance, but the results command more respect when they are essentially duplicated by many different groups using different methods of approach, prospective as well as retrospective studies, working in different parts of the same country and in at least four different countries. Additional confirmation is obtained if analysis of subgroups of a major study gives harmonious results, as reported by Doll [4] and by Wynder and Cornfield [17] in their study of physicians in this country. Smoking would explain the variation in frequency of pulmonary carcinoma in the sexes and in areas of different densities of population as well as or better than any alternative suggestion on the basis of currently proved facts.

Even if such an association is shown, as many have pointed out, this does not necessarily prove that smoking causes the cancer. Theoretically the cancer might cause smoking, or both might be dependent upon some unknown third factor. This would have to bear a linear relationship to the factor which makes a man smoke in his twenties and to that which produces a carcinoma of the lung (but almost nowhere else) 30 years later, something which, as Doll has remarked, it is difficult to envisage. Suggestions have been made to search for some constitutional difference, physical or emotional. Smokers have been dubbed a self-selected group, selected as a result of their emotional reactions or the type of their personality. Obviously there must be some inherent difference which makes a minority of subjects exposed susceptible to these carcinogens, whatever they may be, but we shall probably have a long wait before this feature is elucidated. Studies of personality have been urged and are not to be decried. If, however, one distrusts the ability of a questioner of average intelligence to get an unbiased account of whether a subject smokes and, if so, how many cigarettes a day and for how long, the chance seems dim indeed of getting a useful and unbiased account of their personality and emotional status. The available evidence at present makes it seem more reasonable to postulate a direct causal relationship.[3]

Even if this is accepted, it does not eliminate the possibility that atmospheric pollution is also important,[6, 8] and under some circumstances may be more so than smoking. The means (carcinogens) and the opportunity

(widely distributed pollution of the atmosphere) are at hand, but direct proof of their activity in man seems even harder to secure than in the case of smoking. With our mobile populations it is difficult to get adequate control groups with any assurance that they have not been significantly exposed. The confusing effects of smoking must also be avoided. If such exposure was a major cause of cancer, high rates would be expected in occupational groups most heavily exposed, such as railroad train men and yard men, workers in oil fields and refineries, garages and service stations, bus and truck drivers. No clear-cut increase in such groups has as yet been convincingly demonstrated.[3, 24, 25] Doll [3] found some increase in workers in gas manufacturing plants, in a ratio of 23:14, not a highly impressive figure, but not in the other occupations analyzed. Further study along these lines is obviously needed.

How great is the risk from smoking? To assess quantitatively a tendency whose actual existence is questioned is a precarious procedure. If the reported figures are reasonable approximations, however, some estimate is possible. On the basis of Doll's study of pulmonary cancer in nonsmokers, he estimated that of five deaths in males from 25 to 75 years of age in 1950, lung cancers in four were attributable to smoking and in one to some other cause.[23] Among heavy smokers (25 or more cigarettes a day) over 50, the incidence of pulmonary cancer in the studies reviewed by Haenszel [21] was 13 times that in nonsmokers; in Breslow's,[1] 25 times; and in Doll's, 50 times.[4] On the basis of the death rate from pulmonary cancer of 4% in males 45 to 64 years of age, reported by Breslow [1] in California, and a similar figure by Doll in Great Britain, one may estimate that about three out of 100 men who reach this age will die of pulmonary carcinoma during these decades but might have escaped it if they had not smoked.

Such figures are manifestly merely approximations. They do not justify ill considered or precipitate action, pending more precise information. They do seem adequate, however, to use in advising our patients of the approximate danger which now appears inherent in the habit. They make no less important further studies of the direct effect of atmospheric pollution and the use of all reasonable measures to check the reckless discharge of carcinogens and other toxic substances into the atmosphere.

PAUL W. CLOUGH, M.D.

[24] Haenszel, W.: Epidemiological tests of theories of lung cancer etiology, Pub. Health Rep. **71**: 163–172, 1956.

[25] Wynder, E. L., and Graham, E. A.: Etiologic factors in bronchogenic carcinoma with special reference to industrial exposures, Arch. Indust. Hyg. **4**: 221–235, 1951.

REVIEWS

Annual Review of Medicine. Vol. 7. WINDSOR C. CUTTING, Editor; HENRY W. NEWMAN, Associate Editor. 490 pages; 23 × 15.5 cm. Annual Reviews, Inc., Stanford, California. 1954. Price, $7.00.

The current issue of this valuable yearly publication contains more than 3,100 references to the pertinent literature in the subdivisions reviewed. This massive bibliography, while in no way considered to be a complete review of all the literature, permits a wide sampling of the available writing on a variety of medical subjects. Even so, there are certain limitations, because of selection of subjects, so that many fields of interest are not covered in this volume.

Radiobiology receives a prominent share of the attention of reviewers, being represented in two main fascicles and obviously influencing other sections. The newer concepts of immunity are analyzed in clear terms, and the possibilities for research in this broad field are discussed. In recent issues of the *Annual Review* considerable space has been apportioned to the functional aspects of lung disease, and the present volume includes a clearcut analysis of the pressing widespread problem of pulmonary emphysema. The prospectus for Volume 8 promises the interested public an over-all clinical picture of respiratory diseases, to be reviewed by Dr. J. Burns Amberson. The renal section deals with recent advances in the clarification of renal disease by needle biopsy of the kidney. Important features of effects of the administration of narcotic and anesthetic agents on the kidney are considered and placed in their proper perspective. These may influence the outcome of surgical treatment considerably.

The endocrinology portion is devoted to recent advances in hormone physiology. The diagnostic and therapeutic implications in this rapidly expanding, highly technical field are very clearly delineated. The surgical and medical features of cardiovascular disease are critically treated.

In addition to the specifically noted segments, several other extensive sections are included. Finally, there is an annotated review of review articles, comprising 893 separate additional references.

This series of books, now being published in several different disciplines, is of inestimable help to the clinician, the student, the teacher, and the investigator. The current volume should be available to all interested in the field of medicine, no matter what segment.

J. E. C.

Diseases of the Thyroid Gland. By SAMUEL L. GARGILL, M.D., Assistant Clinical Professor of Medicine, Harvard Medical School; Consultant to Endocrine Clinic, and Head of the Fertility Clinic, Beth Israel Hospital, Boston, Mass.; and MARK FALCON LESSES, M.D., Instructor in Medicine, Harvard Medical School; and Director of Blood Bank, Beth Israel Hospital, Boston, Mass. 490 pages; 24.5 × 18 cm. Oxford University Press, Inc. New York 11, N.Y. 1955. Price, $12.00.

Although the medical book shelves have been flooded in recent years with a number of monographs and discussions dealing with the thyroid gland and its diseases, there always seems room for a truly authoritative text in this field. Drs. Gargill and Lesses have drawn from their clinical experiences over the past 25 years

in order to present this comprehensive and well arranged text which encompasses three important eras in thyroid disease, namely the utilization of stable iodide, the use of antithyroid compounds and the more recent and exciting prospects unveiled by the application of radioactive iodine as an investigative and therapeutic tool in the study of thyroid disorders.

The present edition of this work was reprinted from the Oxford Loose-leaf Medicine Volumes of 1954 with the same page numbers as that work, thus producing a pitfall for the unwary reader. Such a point is minor and does not detract from the value of the material presented.

There are some eight different parts to the book organized into standard divisions. They are: anatomy and physiology of the thyroid gland and relationship of the thyroid to other endocrine glands. The metabolism of iodine and mechanisms of action of the anti-thyroid compounds and their rôle in the investigation of thyroid physiology is next taken up. Part V begins the classification of diseases of the thyroid and is given almost entirely to methods and means of thyroid diagnosis. The laboratory diagnostic tools are quite thoroughly, and at times, extensively discussed. The remainder of the book is devoted to such things as non-toxic goiter, toxic goiter, myxedema, thyroiditis, and finally benign and malignant neoplasms of the thyroid.

The subject matter is well presented, in bold type thus making reading easier. There are many black-and-white illustrations, charts, diagrams, and pathology reproductions. One particularly appealing aspect is the excellent bibliography which appears after each chapter.

Taking all aspects into consideration it appears that Drs. Gargill and Lesses have done well in presenting yet another learned presentation on disorders of the thyroid gland. The addition of this text to the already available material on the subject should prove to be of great value to the physician reader.

J. B. W.

High Blood Pressure. By GEORGE WHITE PICKERING, M.A., M.B. (Cantab.), M.D. (Ghent), F.R.C.P. 547 pages; 24.5 × 15.5 cm. Grune and Stratton, New York. 1955. Price, $9.50.

The true observer after toiling with his insolvable problem, will in time summarize his experiences as a focus for further investigation. Such is the nature of this volume. Dr. Pickering's purpose is "to explain his views on the pathogenesis and cause of essential hypertension and to relate them to established knowledge." This he has done in a frank and fresh manner. The author explores problems in all their aspects, then clearly presents evidence in support of his convictions. Throughout the book there is developed a physiological approach to "the new" concept that the difference between normal blood pressure and raised blood pressure of essential hypertension is quantitative and not qualitative. Malignant hypertension is the severe expression of this quantity. The natural history and epidemiology of high blood pressure are stressed while de-emphasizing the concept of a sharp division between normal blood pressure and hypertension.

Disappointing is the omission of the promised discussion (page 313) concerning prostatic obstructive uropathy as a curable cause of hypertension. Alphabetical listing of references is disconcerting.

This book will have its greatest appeal to students and practitioners rather than to the vascular investigator already familiar with the philosophy of Dr. Pickering.

F. J. B.

Anesthesia for Obstetrics: Labor, Delivery, Infant Care. By ROBERT A. HINGSON and LOUIS M. HELLMAN. 344 pages; 26 × 18 cm. J. B. Lippincott Co., Philadelphia. 1956. Price, $12.50.

In 1944 Lull and Hingson published "Control of Pain in Childbirth," the first combined efforts of an anesthesiologist and an obstetrician to present the peculiar problems of anesthesia in obstetrics. Their three editions were widely accepted because of their specialized values to the combined fields.

Hingson and Hellman's recent volume has enlarged upon, refined and added to this former work and many will recognize the older book as the basis for this new one. Quite a large amount of new material and ideas have been added particularly in the field of psychological principles of pregnancy and delivery, the evaluation by the patient of anesthetic practices and the reporting of the excellent work done by a team of anesthesiologists, obstetricians, nurses and biostatisticians in the evaluation of anesthetic practices at time of delivery at the Johns Hopkins Hospital.

Anatomic and physiologic considerations are dwelt upon in detail; technics of administration of all types of anesthesia are considered and evaluated; recommendations as to type of anesthesia in various maternal and fetal complications are of practical value and well worth consideration; anesthetic obstetric mortality and prenatal morbidity and mortality in different anesthesias are noted; maternal and infant safeguards are nicely discussed by Dr. Virginia Apgar; and finally, the organization of an obstetric anesthetic service on a 24 hour basis is described.

There is no greater need in American obstetrics today than better liaison and understanding of these two closely associated disciplines. Many phases of obstetric anesthesia differ remarkably from general surgical anesthetic technics. It behooves both anesthesiologists and obstetricians to formalize better liaison and understanding of the problem and, thereby, better safeguards for the mother and infant around birth.

This is an important volume. All anesthesiologists and obstetricians are urged to read and absorb it.

D. FRANK KALTREIDER

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Clinical Examinations in Neurology. By MEMBERS OF THE SECTIONS OF NEUROLOGY AND SECTION OF PHYSIOLOGY, Mayo Clinic and Mayo Foundation for Medical Education and Research, Graduate School, University of Minnesota, Rochester, Minnesota. 370 pages; 24.5 × 16 cm. 1956. W. B. Saunders Company, Philadelphia. Price, $7.50.

EKG-Fibel. By DR. MED. ROLF HEINECKER; mit einem Geleitwort von PROF. DR. FERDINAND HOFF. 203 pages; 23 × 15.5 cm. (paper-bound). 1956. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, kartoniert DM 19.80.

Epileptic Seizures: A Correlative Study of Historical, Diagnostic, Therapeutic, Educational and Employment Aspects of Epilepsy. Based on proceedings of joint meetings of The Seventh Western Institute on Epilepsy, the Western Society of Electroencephalography, and the American Academy of General Practice (Arizona chapter) on November 10, 11, 12, 1955 in Phoenix, Arizona. JOHN R. GREEN, M.D., and HARRY F. STEELMAN, M.D., Editors. 165 pages; 24 × 16 cm. 1956. The Williams & Wilkins Company, Baltimore. Price, $5.00.

Expert Committee on Insecticides: Sixth Report. World Health Organization Technical Report Series No. 110. 88 pages; 24 × 16 cm. (paper-bound). 1956. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 60¢.

Functions of Autonomic Transmitters. The Abraham Flexner Lectures, Series Number Thirteen. By J. HAROLD BURN, M.D., The Professor of Pharmacology, Oxford University, England. 228 pages; 21 × 14 cm. 1956. Published for Vanderbilt University by The Williams & Wilkins Company, Baltimore. Price, $5.00.

Medical Aspects of Traffic Accidents: Proceedings of the Montreal Conference, 1955. HAROLD ELLIOTT, M.D., Editor. 519 pages; 24 × 16 cm. 1955. The Traffic Accident Foundation for Medical Research, Montreal. Price, $7.00 (plus 25¢ postage).

Morals in Medicine. By THOMAS J. O'DONNELL, S. J., Regent and Professor of Medical Ethics, Georgetown University School of Medicine, Georgetown University Hospital. 281 pages; 22.5 × 14 cm. 1956. The Newman Press, Westminster, Maryland. Price, $3.75.

The Nature of Brucellosis. By WESLEY W. SPINK, M.D., D.Sc. 464 pages; 24 × 16 cm. 1956. The University of Minnesota Press, Minneapolis. Price, $8.00.

Pediatrics. Edited by DONALD PATERSON, M.D., Formerly Clinical Professor, Department of Pediatrics, The University of British Columbia; and JOHN FERGUSON MCCREARY, M.D., Professor and Head, Department of Pediatrics, The University of British Columbia; with 36 contributing authors. 654 pages; 26 × 18 cm. 1956. J. B. Lippincott Company, Philadelphia. Price, $14.00.

Proceedings of the Annual Meeting, Council for High Blood Pressure Research, American Heart Association, Cleveland, Ohio, November 18–19, 1955. Volume IV. 186 pages; 23.5 × 15 cm. 1956. American Heart Association, New York. Price, $4.50.

Toxic Hazards of Pesticides to Man: Report of a Study Group. World Health Organization Technical Report Series No. 114. 51 pages; 24 × 16 cm. (paper-bound). 1956. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 60¢.

Tuberculosis Control: Plans for Intensified Inter-Country Action in Europe: Report of a Study-Group. World Health Organization Technical Report Series No. 112. 14 pages; 24 × 16 cm. (paper-bound). 1956. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

The Year Book of Medicine (1956–1957 Year Book Series). Edited by PAUL B. BEESON, M.D., CARL MUSCHENHEIM, M.D., WILLIAM B. CASTLE, M.D., TINSLEY R. HARRISON, M.D., FRANZ J. INGELFINGER, M.D., and PHILIP K. BONDY, M.D. 744 pages; 20 × 13.5 cm. 1956. The Year Book Publishers, Incorporated, Chicago. Price, $6.75.

COLLEGE NEWS NOTES

38TH ANNUAL SESSION, A.C.P., BOSTON, MASS., APRIL 8–12, 1957

The Scientific Program has been filled since the meeting of the Program Committee on November 10, 1956. The Committee received approximately 300 proffered titles and abstracts. Sifting and selecting the papers was a Herculean task; many excellent titles could not be used because of the limited number of open appointments on the program.

A most excellent program of hospital clinics, color televised presentations, clinical pathological conferences, clinical physiological conferences, clinical biochemical conferences and panel discussions have been set up. While there will be no formal scientific exhibit at Boston, there will be one of the finest technical exhibits the College has ever had.

The meeting will take on some international aspect in view of the appearance of several distinguished foreign guests on the program, including Dr. E. G. Sayers, President of the Royal Australasian College of Physicians, Lord Cohen of Berkenhead, England, and Professor Hans Heinrich Berg of Hamburg, Germany.

Among the entertainment features will be a concert in Boston Music Hall by the Boston Symphony Orchestra on Monday evening, a reception to new members and their wives at the Boston Art Museum on Tuesday evening, the Annual Convocation on Wednesday evening, and the Annual Banquet on Thursday evening. At the Convocation, Dr. Walter L. Palmer will deliver the presidential address; Fellowships will be conferred on approximately 300 new Fellows; Honorary Fellowships will be conferred on some of the eminent foreign guests; Masterships will be awarded to three distinguished Fellows of the College; the Annual Awards will be made for the Phillips Memorial Medal in Internal Medicine, the Bruce Memorial Medal in Preventive Medicine, and the Alfred Stengel Memorial Certificate (a service award).

Hotel accommodations: A list of official hotels will be published in the formal program. The Hotel Statler and the Hotel Sheraton Plaza will be official Headquarters. The Boston Convention Bureau will operate the Housing Bureau for this meeting. Formal reservation forms are available through the Executive Offices of the College and a copy will be enclosed to every member with the final program.

All scientific meetings will be held in Mechanics' Building on Huntington Avenue, with the exception of a few of the panel discussions and the hospital clinics.

The program will be published in the February, 1957, issue of this journal. Additionally, a final and separate program will be published and distributed to every member of the College and to all non-members on a special mailing list. Any interested physician may be entered on the special mailing list on request to the Executive Secretary, 4200 Pine St., Philadelphia 4, Pa.

NEW ELECTIONS TO MEMBERSHIP IN THE AMERICAN COLLEGE OF PHYSICIANS

On November 10, 1956, the Board of Regents, on recommendation of the Committee on Credentials, provided for the following elections. Those listed in FULL CAPITALS were elected to Fellowship; those in lower case were elected to Associateship.

Robert Saul Aaron ..... Great Neck, N. Y.
Charles Valloyd Adair ..... Mansfield, Ohio
DANIEL K. ADLER ..... Syracuse, N. Y.
MORRIS ALEX ..... St. Louis, Mo.

Ralph William Alexander ..... Ithaca, N. Y.
James William Allee ..... Columbia, Mo.
Arthur William Allen ..... Ann Arbor, Mich.
#EARL HENRY ANTES ..... Evansville, Ind.
Henry A. Arkless ..... Philadelphia, Pa.
William Owen Arnold ..... Temple, Tex.
Kurt William Aumann ..... Corvallis, Ore.

Norman Ferdinand Bach ..... Owosso, Mich.
KENNETH PAUL BACHMAN ..... M.C., U. S. Navy
Glenn Dean Baird ..... U. S. Air Force, M.C.
William Cecil Baker ..... Tonawanda, N. Y.
SEYMOUR SAMUEL BALKIN ..... Forrest Hills, N. Y.
R. Stanley Bank ..... Harrisburg, Pa.
EARL STEPHENS BARKER ..... Philadelphia, Pa.
Bernard Barshay ..... Castle Point, N. Y., (VA)
WILLIAM HENRY BATES ..... Cottonwood, Ariz.
Hugh Miller Batson, Jr. ..... New Orleans, La.
FRANZ KARL BAUER ..... Los Angeles, Calif.
JERE MARKLEE BAUER ..... Ann Arbor, Mich.
Gerald Leonard Baum ..... Cincinnati, Ohio
ROBERT METTLER BECKER ..... Madison, Wis.
Floyd Matere Beman ..... Columbus, Ohio
William Bancroft A. Bentley ..... Waterbury, Conn.
MAX BERG ..... Chicago, Ill.
‡DELBERT MAURITZ BERGENSTAL ..... Chicago, Ill.
Leonard Bernard Berman ..... Washington, D. C.
JACK ABE BERNARD ..... El Paso, Tex.
Elmer I. Bernstein ..... Chicago, Ill.
ROBERT MONTGOMERY BIRD ..... Oklahoma City, Okla.
Edward Welles Bixby, Jr. ..... Philadelphia, Pa.
Arnold Black ..... Chicago, Ill.
Frank McFaden Blanton ..... Richmond, Va.
MARVIN BLUM ..... Wilkes-Barre, Pa.
William Frederick Boehm ..... Chicago, Ill.
Willard Henry Boggan, Jr. ..... Jackson, Miss.
Abraham Bogoch ..... Vancouver, B. C., Canada
MARTIN HAROLD BOLDT ..... Louisville, Ky.
ROBERT E. BOLINGER ..... Kansas City, Kans.
Robert Donnell Bone ..... Corsicana, Tex.
Herbert Spencer Bowman ..... Harrisburg, Pa.
LYMAN CROWELL BOYNTON ..... Rochester, N. Y.
EARL PHILLIP BRANNON ..... Perry Point, Md., (VA)
Harry Harris Brill ..... Columbus, Ga.
Bernard Noah Brodoff ..... Tuckahoe, N. Y.
Sidney Irving Brody ..... M.C., U. S. Navy
RANDOLPH KELLEY BROWN ..... Washington, D. C.
EDWARD GRAY BROWNELL ..... Winnipeg, Man., Canada
MICHAEL S. BRUNO ..... New York, N. Y.
Delbert Milo Buchman ..... La Crosse, Wis.
Joseph Stewart Burkle ..... M.C., U. S. Navy

#(MC) AUS.
‡USPHS (R).

Thomas Alfred Callister ..... Pasadena, Calif.
Roscoe Patrick Carney ..... Davenport, Iowa
Edward Albert Carr, Jr. ..... Ann Arbor, Mich.
Richard Devore Carter ..... Birmingham, Ala.
RAY LLEWELLYN CASTERLINE ..... Medford, Ore.
Robert Franklin Cech ..... Iowa City, Iowa, (VA)
Benjamin Chernoff ..... Philadelphia, Pa.
ROBERT BRUNO CHODOS ..... Fayetteville, N. Y., (VA)
EDWARD RAYMOND CHRISTIAN ..... New Orleans, La.
Joseph Ralph W. Christian ..... Chicago, Ill.
Charles Bernard Clayman ..... Chicago, Ill.
John Gordon Claypool ..... Kansas City, Kans.
Thomas Carlaw Clifford ..... Pittsfield, Mass.
JOSEPH SULLIVAN CLUTTER ..... Pueblo, Colo.
Aaron Arthur Cohen ..... San Fernando, Calif., (VA)
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George Warner Collen ..... Inglewood, Calif.
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BRANCH CRAIGE ..... El Paso, Tex.
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RALEIGH ROBERT CURTIS ..... Temple, Tex.
VERNON DALE CUSHING ..... Oklahoma City, Okla.

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Bernard David Epstein ..... Cleveland, Ohio
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Marvin Allen Epstein .....Walnut Creek, Calif.
Stanleigh Erler .....Whittier, Calif.

Joseph Shearer Fager .....Harrisburg, Pa.
Harold Irwin Farber .....Reading, Pa.
Robert Bernard Fath .....Scarsdale, N. Y.
Donald Moss Finlayson .....Toronto, Ont., Canada
Allan James Fleming .....Wilmington, Del.
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Hugh Vernon Freidell .....Santa Barbara, Calif.
Leo Burton Froke .....Grand Forks, N. D.
David Crozier Funk .....Iowa City, Iowa, (VA)

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Royal Rotter ..... Madison, Wis.
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PAUL NANGAN YU .....Rochester, N. Y.
ANTON STANLEY YUSKIS .....San Diego, Calif.

Henry Edward Zellmann .....Boston, Mass.
Desiderius Igor Zubritzky .....McKeesport, Pa.
GARY ZUCKER .....New York, N. Y.

Gifts to College Library of Publications by Members

The College gratefully acknowledges receipt of the following autographed books by members of the College for the Memorial Library of the College:

John R. Graham, M.D., F.A.C.P., Boston, Mass., *Treatment of Migraine,* published by Little, Brown, and Company, Boston, Toronto, 1956; 149 pages.

Francis M. Rackemann, M.D., F.A.C.P., Boston, Mass., *The Inquisitive Physician: The Life and Times of George Richards Minot, M.D.,* published by Harvard University Press, Cambridge, Mass., 1956; 288 pages.

Wesley W. Spink, M.D., F.A.C.P., Minneapolis, Minn., *The Nature of Brucellosis,* published by The University of Minnesota Press, Minneapolis, 1956; illustrated, 464 pages.

U. S. von Euler, M.D., F.A.C.P., (Hon.), Stockholm, Sweden, *Noradrenaline,* published by Charles C Thomas, Publisher, Springfield, Ill., 1956; illustrated, 382 pages.

Hawaiian Regional Meeting, A.C.P.

A Regional Meeting of the American College of Physicians in Hawaii was held Oct. 10, 1956, at the Tripler Army Hospital in Honolulu, under the Chairmanship of Dr. Nils P. Larsen, F.A.C.P., Governor. About 30 physicians were in attendance. Three papers were presented: One, an excellent one with slides on the new method of peritoneal dialysis, developed by Tripler Hospital and presented by Dr. Hern; the second was a general round table in which every attendant took part, regarding the present knowledge of fluoridation. There has been considerable controversy on the Island concerning fluoridation, and the community has turned down the proposition although the Services have gone ahead and fluoridated their own water. The last paper was a report by Dr. Larsen on a field study on atherosclerosis based on a paper he gave at the Nevada State Medical Association Meeting in Reno last August.

Col. Wilbur C. Berry (Associate), who is the Head of the Medical Service at Tripler Army Hospital, extended an invitation to the group to hold their meetings at that Hospital in the future.

Certifying Board Examinations

American Board of Internal Medicine—William A. Werrell, M.D., Secretary-Treasurer, 1 West Main St., Madison 3, Wis.

Written examination, Oct. 21, 1957; closing date for applications, May 1, 1957.
Oral examination (Boston), April 3, 4, 5, 6, 1957; (New Orleans), Feb. 5, 6, 7, 8, 1957. There will be oral examinations also in June and September of 1957, but dates have not yet been specified.

The American Board of Pathology—Edward B. Smith, M.D., Secretary-Treasurer, 1040–1232 West Michigan St., Indianapolis 7, Ind.

Washington, D. C., April 4, 5, 6, 1957; closing date for applications, March 1, 1957.

The American Board of Pediatrics—John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Road, Rosemont, Pa.

Written examination, January 11, 1957.
Oral examinations: (New Orleans, La.), Feb. 22, 23, 24, 1957; (Washington, D. C.), April 4, 5, 6, 1957; (San Francisco, Calif.), June 21, 22, 23, 1957; (Chicago, Ill.), Oct. 11, 12, 13, 1957; (Boston, Mass.), Dec. 6, 7, 8, 1957.

American Board of Physical Medicine and Rehabilitation—Earl C. Elkins, M.D., Secretary-Treasurer, 200 First St., S.W., Rochester, Minn.

Part I and Part II examinations (New York City, N. Y.), June 8, 9, 1957.

The American Board of Preventive Medicine—Ernest L. Stebbins, M.D., Secretary-Treasurer, 615 North Wolfe St., Baltimore 5, Md.

The last examination was held in Philadelphia, November, 1956. Announcement of the dates for the 1957 examinations will be made in the near future.

American Board of Psychiatry and Neurology—David A. Boyd, Jr., M.D., Secretary-Treasurer, 102–110 Second Ave., S.W., Rochester, Minn.

(New Orleans, La.), March 18, 19, 1957.

A.C.P. Coming Regional Meetings

Territory	Date 1957	City	Governor(s)	Special Guest
MARYLAND–DISTRICT OF COLUMBIA	Jan. 12	Washington	John Minor, M.D. R. C. Tilghman, M.D.	Walter L. Palmer, M.D., President
OHIO	Jan. 17	Dayton	Chas. A. Doan, M.D.	Walter L. Palmer, M.D., President
COLORADO	Jan. 18–19	Colorado Springs	C. F. Kemper, M.D.	Richard A. Kern, M.D., President-Elect
EASTERN PENNSYLVANIA	Jan. 18	Philadelphia	T. M. McMillan, M.D.	Irving S. Wright, M.D., Governor, Eastern N. Y.
DELAWARE	Feb. 9	Wilmington	L. C. McGee, M.D.	Richard A. Kern, M.D., President-Elect
MISSOURI	Feb. 23	St. Louis	C. V. Moore, M.D.	Walter L. Palmer, M.D., President
SO. CALIFORNIA	Feb. 23–24	Santa Barbara	G. C. Griffith, M.D.	Howard P. Lewis, M.D., Regent
VIRGINIA	March 2	Williamsburg	C. M. Caravati, M.D.	Richard A. Kern, M.D., President-Elect
KANSAS	March 15	Topeka	W. C. Menninger, M.D.	Richard A. Kern, M.D., President-Elect

Not only are Fellows and Associates of the College cordially invited to attend these meetings, but also any physician who is interested in the field of internal medicine and in any particular program. Ordinarily programs are mailed only to the members and candidates for membership in the state or states included in the meeting, but interested physicians from any locality will be sent a program on request to the Executive Secretary, 4200 Pine Street, Philadelphia 4, Pa.

The American Board of Radiology—B. R. Kirklin, M.D., Secretary-Treasurer, Kahler Hotel Bldg., Rochester, Minn.

Oral examinations: (Tampa, Fla.), April 2–6, 1957; (Washington, D. C.), Sept. 24–28, 1957.

1956 Nobel Award in Medicine

On October 18, the 1956 Nobel Prize in Medicine was awarded jointly to Dr. Dickinson W. Richards, Jr., F.A.C.P., New York City, Dr. Andre F. Cournand, 1952 recipient of the John Phillips Memorial Medal of the American College of Physicians, New York City, and Dr. Werner Forssmann, of Bad Kreuznack, West Germany. The award, under the will of the inventor of dynamite, the late Alfred Nobel, is made by the Caroline Institute of Medicine and Physiology. According to the citation, the prize was given in recognition of "the introduction of heart catheterization and discoveries made thereby." The awards were presented in Stockholm on December 10. The recipients will divide prize money totaling $38,633.

Conference on Atherosclerosis and Coronary Heart Disease

Dr. Robert L. Levy, F.A.C.P., is Chairman of the Steering Committee, organizing a one-day Conference on Atherosclerosis and Coronary Heart Disease, at the Waldorf-Astoria Hotel, New York City, January 15, 1957, the conference being sponsored by the New York Heart Association.

Speakers will include Dr. Paul Dudley White, M.A.C.P., Boston, Dr. E. Cowles Andrus, F.A.C.P., Baltimore, Dr. Howard A. Rusk, F.A.C.P., New York City, and others. Dr. A. Wilbur Duryee, F.A.C.P., President of the New York Heart Association, will preside at the luncheon.

Seventh International Cancer Congress

The Seventh International Cancer Congress, sponsored by the International Union Against Cancer, will be held in London, England, July 6–12, 1958, under the Presidency of Sir Stanford Cade. Congress headquarters will be The Royal Festival Hall. There will be two main sessions of the Congress: (a) Experimental; (b) Clinical and Cancer Control. Special emphasis will be placed on Hormones and Cancer, Chemotherapy, Carcinogenesis, and Cancer of the Lung.

Registration fee for the Congress will be £10 (ten pounds) or $30.00, and the latest date for registration without late fee will be January 1, 1958.

Registration forms and a preliminary program will be available early in 1957 on application to The Secretary General, Seventh International Cancer Congress, 45 Lincoln's Inn Fields, London, W. C. 2, England.

VIII International Congress of Paediatrics

The VIII International Congress of Paediatrics was held at Copenhagen, Denmark, July 22–27, 1956. The proceedings were published, including Exhibition Catalogue, 130 pages; Abstracts of Papers, 148 pages; and Discussions, about 176 pages. Active members of the Congress will receive the book of discussions free; others may obtain the complete set of books on subscription to: VIII International Congress of Paediatrics, c/o J. Vesterdal, M.D., University Clinic of Paediatrics, Rigshospitalet, Copenhagen, Denmark.

Fifty-Third Annual Congress on Medical Education and Licensure

The Annual Congress on Medical Education and Licensure is conducted under the auspices of the Council on Medical Education and Hospitals of the American Medical Association, the Federation of State Medical Boards of the United States and the Advisory Board for Medical Specialties. The Fifty-Third Annual Congress will be held at the Palmer House, Chicago, Feb. 10–12, 1957.

On February 10, there will be a special program in graduate medical education for general practice; in the afternoon of February 10 will be held the business meeting of the Advisory Board for Medical Specialties, as well as an open meeting of the Federation of State Medical Boards of the United States. On February 11, "Medical Education Tomorrow" will be held as a symposium in the morning, and in the afternoon there will be a conference on "Postgraduate Medical Education" and methods of meeting some of its challenges. On Tuesday, February 12, will be given the program of the Federation of State Medical Boards of the United States developed around the general theme "Reëvaluation of the Licensing Examination."

Stover Report, Joint Commission on Accreditation of Hospitals

The so-called "Stover" Commission appointed by the American Medical Association House of Delegates, to review the functions of the Joint Commission on Accreditation of Hospitals, concluded its examination at a conference during the past year, and its report was approved by the House of Delegates in June, 1956.

The conclusions of the Committee were as follows:

1. Accreditation of hospitals should be continued.
2. The Joint Commission should maintain its present organizational representation.
3. The Board of Trustees should report annually to the House of Delegates on the activities of the Joint Commission.
4. Physicians should be on the administrative body of hospitals.

The detailed and complete report of the "Stover" Committee was published in the Journal of the American Medical Association, Nov. 3, 1956.

Markle Fund Continues Medical School Faculty Grants for Tenth Year

The Markle Foundation has announced that it will continue for the tenth year its program of five-year grants for young medical school faculty members seeking careers in academic medicine. The Fund's Grants for Scholars in Medical Science were first offered in 1948 to give academic security and financial help to selected teachers and investigators. During the nine years of the program a total of $5,320,000 has been appropriated toward the support of 181 doctors in 69 medical schools in the United States and Canada.

Approximately two thirds of the Scholars have taught and conducted research in the clinical sciences, and approximately one third are teachers and investigators in the preclinical sciences.

For the past year the income for the Foundation totalled more than $1,000,000. The largest allocation, $690,000, was appropriated for support of twenty-three Scholars in Medical Science, at the rate of $6,000 a year for five years, including those at medical schools in the following institutions: Columbia, Florida, Pittsburgh, Duke, Queen's University (Canada), Yale, Harvard, Maryland, Wisconsin, and the Universities of California (San Francisco and Los Angeles). Three other grants

were made in the field of medical science. The sum of $75,000 was given to Northwestern University Medical School for a three-year study of an integrated program between preprofessional and professional training in medicine; and $115,000 was appropriated to the National Research Council Division of Medical Sciences, of which $15,000 is for a study to determine whether an adequate number of young medical men and other scientists are being trained in research technics in the health sciences, and $100,000 is for support of the Council's fellowship program during the study.

The Markle Foundation was established in 1927 by John Markle, Pennsylvania coal operator, with an initial endowmen of $3,000,000 which increased under the terms of his will to approximately $16,000,000. Grants for Scholars in Medical Science are now the major program of the Fund.

1957 Mississippi Valley Medical Society Essay Contest

Any subject of general medical or surgical interest, including medical economics and education, may be submitted provided the paper is unpublished and is of interest and applicable value to general practitioners of medicine. Contributions are accepted only from physicians who are members of the A.M.A. and who are residents and citizens of the United States. Manuscripts must not exceed 5,000 words and must be submitted in five complete copies, in manuscript style. The winning essay receives a cash prize of $100.00, gold medal, and a certificate, also an invitation to address the annual meeting of the Mississippi Valley Medical Society (1957—St. Louis, Mo., Sept. 25–27). The Society may also award certificates of merit to physicians whose essays rate second and third best. Further details may be secured from Dr. Harold Swanberg, F.A.C.P., 209–224 W. C. U. Building, Quincy, Ill.

Mid-Winter Heart Symposium

The Mid-Winter Heart Symposium of the Los Angeles County Heart Association will be held in the Los Angeles County Medical Association Auditorium, Los Angeles, Calif., January 23, 1957, according to Dr. Edward Phillips, F.A.C.P., of the Professional Education Committee. Short papers on all phases of cardiovascular diseases, including the basic sciences, will be presented.

Aero Medical Association, 1957 Meeting

Medicine in the jet-atomic age of flight will be the central theme of the 28th annual meeting of the Aero Medical Association in Denver, May 6–8, 1957, under the presidency of Dr. Jan H. Tillisch, F.A.C.P., Rochester, Minnesota, Medical Director of Northwest Airlines. The scientific program will include reports on emergency escape from high performance aircraft, new developments in airline passenger comfort and safety, and current research in manned space satellites. The American Board of Preventive Medicine will conduct examinations for certification in aviation medicine in Denver, May 3–5.

Special events include the third Louis H. Bauer (F.A.C.P.) Lecture, established in 1954 as a living tribute to the founder and first president of the Association, presentation of the Lister, Longacre, and Tuttle Awards, the highest honor in aviation medicine, and an extensive display of scientific exhibits. The first recipient of a new aeromedical medal, sponsored by Charles Pfizer and Company, will also be announced. Dr. Ashton Graybiel, Research Director of the U. S. Naval School of Aviation Medicine, Pensacola, Florida, will be installed in office as President.

Dependents Medical Care Program

On October 18, 1956, the Secretary of Defense, Charles E. Wilson, signed a directive under which the Dependents Medical Care Program will operate beginning December 7, 1956.

The new directive, applicable to all of the uniformed services (Army, Navy, Air Force, Marine Corps, Coast Guard, Coast and Geodetic Survey, and commissioned ranks in the U. S. Public Health Service) outlines the eligibility of dependents to receive the benefits of Public Law 569, 84th Congress; describes the services available; specifies services which are not available under the Act; and prescribes the arrangements and services to be furnished eligible dependents in civilian medical facilities.

Designed to assure hospital care when needed by the wives and children of active duty personnel, the new law contains a provision authorizing the use of civilian hospitals and facilities for the immediate families of servicemen. In addition, medical care for dependents of both active duty and retired personnel in Government facilities will be provided on a space available basis.

Cost to a service family for hospitalization in either a government or civilian facility is limited to a payment of either $25.00 or an amount equivalent to the subsistence charge of $1.75 per day, whichever is greater. This charge covers all hospital services and doctors' fees for the period of hospitalization.

Eligible dependents requesting care at a government facility are expected to use the facilities in the area in which they live. In the Continental United States, Alaska, Hawaii and Puerto Rico, dependents not living with their sponsor who are eligible for civilian care have their choice between government and civilian facilities, unless otherwise directed. If government facilities are adequate and the use of government facilities would be economically practical, the dependents may be directed to use government facilities.

Outpatient service will not be provided to dependents at civilian medical facilities at Government expense, except for maternity patients.

Medical care at government facilities for eligible dependents is limited to: diagnosis; treatment of acute medical conditions; treatment of surgical conditions; treatment of contagious diseases; immunization; obstetrical and infant care; and treatment for acute emergencies of any nature that are a threat to the life, health, or well-being of the patient.

Dental care is not authorized in government facilities except in emergencies, as a necessary adjunct to medical and surgical treatment, outside the Continental United States, or within the Continental United States, where adequate civilian facilities do not exist.

Neither is hospitalization authorized at Government Facilities for chronic diseases; nervous and mental disorders; elective medical and surgical treatment which is not medically essential; nor are domiciliary care, or home calls provided.

Hospital care may be authorized in civilian facilities for treatment of acute medical conditions; treatment of contagious diseases during hospitalization; treatment of surgical conditions only during hospitalization; complete obstetrical and maternity care; 365 days of hospitalization in semi-private accommodations for each admission including all necessary supplies and services furnished by the hospital; services required of a physician or surgeon prior to and following hospitalization for injury or operation; treatment of acute emergencies of any nature which are a threat to life, health, or well-being; diagnostic tests incident to hospitalization and dental care which is a necessary adjunct to medical or surgical treatment.

Standard identification forms are prescribed and will be in use by July 1, 1957. Eligible dependents will be given equal opportunity for medical care, regardless of

service affiliation through cross utilization of the medical facilities of the Army, Navy, Air Force and Public Health Service.

University of Florida's New Medical Sciences Building

The first unit of the J. Hillis Miller Health Center, in connection with the University of Florida's 5 million dollar Medical Sciences Building, was dedicated October 12–13 to "the citizens of Florida and the advancement of medical education and research." Dr. Detlev W. Bronk, President of the Rockefeller Institute for Medical Research and the National Academy of Science, was the guest speaker. Among state, medical and scientific officials attending the ceremonies were representatives of various medical and scientific associations. The new building houses the University's newly formed Colleges of Medicine and Nursing. An eight-floor Teaching Hospital, the second unit of the Health Center, is now under construction adjacent to the Medical Sciences Building and is due to be completed in the Autumn of 1958.

Wisconsin Society of Internal Medicine

The Wisconsin Society of Internal Medicine was organized during 1955 and held its Second Annual Scientific Meeting at Madison, Wisconsin, during 1956.

This Society has developed as a group to further the educational and scientific aspects of the Section of Internal Medicine of the Wisconsin State Medical Society. The main interests of its members are concerned with the scientific aspects of medicine and better understanding of diseases of human beings. Its Committee on Medical Practice will not involve the entire Society membership in debates of socio-economic nature. Unlike many of the other recently organized Societies of Internal Medicine it will not, for the present, affiliate itself with the American Society of Internal Medicine, nor will it stress particularly the economic problems of internists.

Its committees are all headed by members of the American College of Physicians. Its officers for 1956–1957 include Karl H. Doege, M.D., F.A.C.P., President, Marshfield; Robin N. Allin, M.D., F.A.C.P., Vice-President, Madison; Paul J. LaBissoniere, M.D. (Associate), Secretary-Treasurer, Milwaukee; Warren K. Simmons, M.D., F.A.C.P., Rhinelander, Robert L. Gilbert, M.D. (Associate), LaCrosse, and Maurice Hardgrove, M.D., F.A.C.P., Milwaukee, Directors.

Columbus Society of Internal Medicine

The Columbus Society of Internal Medicine has been recently organized with the following officers: President, Donald L. Mahanna, M.D., F.A.C.P.; Vice President, George J. Hamwi, M.D., F.A.C.P.; Secretary-Treasurer, Samuel W. Robinson, M.D.; Councillors, John Prior, M.D., F.A.C.P., George I. Nelson, M.D., (Associate), and Robert Browning, M.D., F.A.C.P.

At a Regional Meeting of the American College of Physicians of Ohio, held at Cincinnati a year ago, a resolution was adopted to the effect that Fellows and Associates of the American College of Physicians in Ohio through their Governor be cordially receptive to any local Ohio Societies of Internists in matters pertaining to regional, professional, economic, and administrative problems, as well as to the practice of internal medicine. Similar societies have been organized in Cleveland, Cincinnati, and other Ohio cities, as elsewhere in the United States.

The manner in which these Ohio city societies of internal medicine have been organized, the Governor of the College and the College can be spokesmen for internists at the state level, and thus further can promote the interests of internal medicine.

New York University Offers Courses

Four courses of interest to the internist, general practitioner, and pediatrician, are being offered by the New York University Post-Graduate Medical School during the month of January. These are included among other courses designed for the specialist and non-specialist.

Modern Concepts in Etiology, Diagnosis and Treatment of Heart Diseases; January 7–11, inclusive; Dr. Charles A. Poindexter, F.A.C.P., Director.

Clinical Internal Medicine; a trimester course held Thursdays from 11:15 A.M. to 4 P.M.; Dr. Charles F. Wilkinson, Jr., F.A.C.P., Director.

Seminar in Dermatology and Syphilology; a course designed for non-dermatologists; January 14–18, inclusive; Dr. Marion B. Sulzberger, F.A.C.P., Director.

Pediatrics Refresher Course; January 14–25, inclusive; Dr. Adolph G. DeSanctis, Director.

New Schering Award Contest

Cardiology, mental disease, and treatment of eye disorders have been selected as topics for the 1957 Schering Award Contest. The competition, which is open annually to all medical students in the United States and Canada, invites the submission of papers on one of these three topics of current medical significance. Established in 1940, this contest has built up a continuing program designed to increase future contributions to professional literature by stimulating student interest in medical communications.

A total of $4,500 in cash prizes will be awarded. A $1,000 first prize and a $500 second prize will be awarded for the best papers on each of the three selected topics. In addition, professionally useful gifts will be offered for other outstanding papers. Award-winning papers will be selected by a group of judges who are authorities in their particular field.

The three subjects for 1957 are: (1) Incidence of Various Types of Cardiovascular Diseases by Age Group in the Male and the Female; (2) Recent Trends in Corticosteroid Therapy for Ocular Disorders; (3) Recent Advances in the Biochemical Aspects and Treatment of Mental Disease.

Literature and entry forms are being distributed in medical schools. Students interested in participating should submit their entry forms by January 1, 1957.

Center for Aging Research

Establishment of a Center for Aging Research in the National Institutes of Health has been announced by Dr. Leroy E. Burney, F.A.C.P., Surgeon General of the Public Health Service, Department of Health, Education, and Welfare. The Center is a part of the Public Health Service's program to coördinate and accelerate all of its activities in the field of aging. Dr. G. Halsey Hunt has been appointed Director of the Center.

New York City Considers "Homesteads" Plan for Patients Not Requiring Active Hospital Care

One out of every five patients in New York City municipal, general and chronic hospitals is there not because he needs hospital services, but simply because he has no place to go, according to a team headed by Dr. Howard A. Rusk, F.A.C.P., after eighteen months' study, financed by the New York Foundation. It was stated that New York City already is taking steps to remedy this situation by the creation of a

number of institutions for such patients, to be known as "homesteads." These new institutions, utilizing existing buildings, will be adjacent to municipal hospitals so that residents in the "homesteads" may be transferred into hospitals should they need medical care from time to time. It is pointed out that the City will save substantial sums and, at the same time, the residents of the "homesteads" will have much richer and fuller lives than they can have in hospitals where they are surrounded by illness and where they must conform to a hospital regimen, which is frequently unrelated to their needs. At the same time, these patients take up the time and efforts of a professional staff whose primary function should be diagnosis, therapy and research, to the detriment of those patients needing these services and at a higher cost than is justified by their actual medical needs.

Dr. Lynwood D. Zinn, F.A.C.P., Clarksburg, was elected Vice President of the West Virginia Heart Association at its Annual Meeting on September 20.

Dr. Walter C. Lobitz, Jr., F.A.C.P., Assistant Professor of Dermatology at Dartmouth Medical School, Hanover, N. H., delivered the first annual Dudley Crofford Smith Lecture in Dermatology at the University of Virginia on October 29, 1956, his title being "Wound Healing Following Experimental Injury in the Human Skin."

Dr. Edgar R. Pund, F.A.C.P., Augusta, Ga., has been appointed by Governor Marvin E. Griffin to serve on the Governor's committee for a work conference on nuclear energy.

Dr. Frederick C. Bauer, Jr., (Associate), Chicago, is the Secretary-Treasurer of the Illinois Society of Pathologists.

Dr. Walter C. Alvarez, F.A.C.P., Chicago, was guest speaker at the 107th Annual Meeting of the Indiana State Medical Association in Indianapolis, October 15–18, his title being "The Minor Variances of Epilepsy."

Dr. James M. Moss, F.A.C.P., Alexandria, Va., was recently promoted to Clinical Associate Professor of Medicine at Georgetown University School of Medicine, Washington. For the past six years Dr. Moss has been the Director of the Diabetic Clinic at Georgetown University Hospital. He is President of the Diabetes Association of the District of Columbia, and is Chairman of the 1956 Diabetes Detection Drive in the Washington metropolitan area, and Vice President of the Medical Society of Alexandria.

Dr. George E. Armstrong, F.A.C.P., Vice President for medical affairs at New York University and Army Surgeon General from 1951 to 1955, was given the Founder's Medal for 1956 by the Association of Military Surgeons of the United States. The presentation was made at the Association's annual Honors Night dinner, held on Nov. 14, at the Hotel Statler in Washington, D. C.

The Founder's Medal is awarded by the Executive Council of the Association to members who have made an outstanding contribution to military medicine and who have given conspicuous service to the Association.

Dr. Armstrong is the holder of numerous awards and decorations, including the Legion of Merit, the Victory Ribbons of both World War I and World War II, and foreign decorations from China, Korea, Italy, France, and Chile.

Dr. J. Arthur Myers, F.A.C.P., Professor of Medicine, Preventive Medicine, and Public Health, University of Minnesota, was awarded the British Varrier-Jones medal for international contributions to tuberculosis knowledge and control during the Fourth International Congress on Diseases of the Chest held at Cologne, Germany, during the past August. The award and a lectureship were established by British physicians as a memorial to Sir Pendrill Varrier-Jones, who promoted a world-famed village near London for tuberculosis patients and their families.

Dr. Raymond M. Galt, F.A.C.P., has been appointed by President Walter L. Palmer an official consultant of the American College of Physicians on the study of medical record library science being conducted by Dr. Antonio Ciocco, Head of the Department of Biostatistics, University of Pittsburgh Graduate School of Public Health.

Dr. Edward J. Stainbrook, F.A.C.P., formerly Professor and Chairman of the Department of Psychiatry, State University of New York College of Medicine at Syracuse, is now Professor of Psychiatry and Chairman of the Department at the University of Southern California School of Medicine, Los Angeles.

Dr. Henry A. Monat, F.A.C.P., Washington, D. C., spoke on "Ulcerative Colitis, the Role of Sprue Diet" at the Convention of the American College of Gastroenterology, Oct. 16, 1956.

Dr. William H. Kelly, F.A.C.P., Richmond, Va., recently resigned as Director of the Memorial Guidance Clinic and Memorial Foundation to accept the position of Assistant Director of the Department of Mental Health in the State of Michigan, as Head of their Mental Hygiene Division. This appointment became effective December 1, 1956.

Dr. Robert H. Ebert, F.A.C.P., formerly Associate Professor of Medicine at the University of Chicago School of Medicine, and Attending Physician at the Albert Merritt Billings Hospital, has accepted a full-time appointment as Professor of Medicine and Director of Medicine of the University Hospitals, Western Reserve University, Cleveland, Ohio.

The Sixth Annual Dr. Ralph Pemberton Memorial Lecture was presented before the Philadelphia County Medical Society, Philadelphia, Pa., on Oct. 31, 1956, by Dr. Leon Sokoloff, Senior Surgeon, U. S. Public Health Service, Research Pathologist, National Institute of Arthritis and Metabolic Diseases, Bethesda, Md. Dr. Sokoloff's title was "The Pathology of Arthritis and Rheumatism." Dr. Sokoloff presented to each of the local medical schools in Philadelphia a set of teaching slides on the Pathology of Arthritis and Rheumatism, as a gift from the Foundation.

Dr. Jack Masur, F.A.C.P., Chief of the Bureau of Medical Services, has become Director of the Public Health Service Clinical Center, located at the National Institutes of Health, Bethesda, Md. Dr. Masur, who supervised the planning and building of the new Clinical Center, assumed his new duties Nov. 1, 1956.

The Clinical Center, largest facility of its kind in the world for research in the major diseases of today, was officially opened in July, 1953. Present facilities are

about to be expanded to permit even greater research in neurological and cardiac surgery. In the three years of its existence, nearly 5,000 patients from all over the United States have been admitted for study and treatment. The Center's facilities for the treatment and care of patients are combined with more than 1,000 specialized laboratories. It is the responsibility of the Director of the Clinical Center to plan and use the facility so that patients will receive the best in medical care and, at the same time, the research programs can be carried forward with maximum effectiveness.

Dr. Harry R. Litchfield, F.A.C.P., New York City, has been elected State Chairman, Section II (Kings, Queens, Nassau and Suffolk) of the American Academy of Pediatrics for the years 1956–59.

Dr. Hugh H. Hussey, F.A.C.P., Washington, D. C., Professor of Medicine and Director of the Department of Medicine, Georgetown University School of Medicine, was guest speaker at the Third Annual Clinic Day at St. Mary's Hospital, Rochester, N. Y., on Oct. 25, 1956. He was clinical discussor at the clinicopathological conference and participated in a conference on peripheral vascular disease.

Dr. David W. Kramer, F.A.C.P., Philadelphia, Pa., presented a paper on the "Management (Medical) of Thrombophlebitis and Post-Phlebitic Syndrome" before the Latin-American Congress of Angiology, at Havana, Cuba, Nov. 7, 1956.

Dr. Aaron E. Margulis, F.A.C.P., Santa Fe, N. M., has been elected Councillor to the New Mexico State Medical Society for a three-year term. He has also been appointed Scientific Editor for New Mexico of the *Rocky Mountain Medical Journal.*

Dr. John R. Walsh, (Associate), has resigned from the Veterans Administration as of Sept. 1, 1956, and has accepted an appointment as Director of the Department of Medicine at Creighton University School of Medicine, Omaha, Nebr.

Dr. Norton M. Luger, (Associate), Fresh Meadows, N. Y., has been appointed Director of Medical Services of a new hospital opened during December, 1956, at Flushing, N. Y.

Dr. G. Gordon McHardy, F.A.C.P., of the Browne-McHardy Clinic, New Orleans, La., was elected President of the American Association of Medical Clinics at its Annual Meeting in Washington, Oct. 26–29, 1956.

Dr. Louis F. Bishop, F.A.C.P., Assistant Clinical Professor of Medicine, Postgraduate Medical School, New York University-Bellevue Medical Center, participated in the recent program of the Third Annual Meeting of the Academy of Psychosomatic Medicine in New York City, his topic being, "Psychosomatic Relationships of General Practice as Related to Heart Disease."

Dr. Bishop also presented a lecture entitled "The Management of Arteriosclerosis in General Practice" as part of the postgraduate course for the general practitioner sponsored by the Medical Society of the County of Kings in association with the Brooklyn Academy of General Practice.

Dr. Richard S. Cosby, F.A.C.P., Pasadena, Calif., addressed the National College of Chest Physicians in Cologne, Germany, August 21, 1956, on the subject, "Abnormal Respiratory Patterns in Left Ventricular Failure."

Dr. George C. Griffith, F.A.C.P., Los Angeles, Calif., spoke on "The Differential Diagnosis of Chest Pain," "The Management of Cardiac Arrhythmias," and "Anticoagulants in Cardiovascular Disease" before the Omaha Mid-West Clinical Society, Omaha, Nebraska, October 31–November 1, 1956.

Dr. Robert Chobot, F.A.C.P., New York, N. Y., presented a lecture before the Pima County Medical Society at Tucson, Ariz., on November 13, 1956, his subject being "The Importance of Infection in Allergy." Dr. Chobot also addressed the Arizona Society of Allergy on November 14, 1956, on the topic, "Diagnostic Measures in Pediatric Allergy."

Dr. Harold A. Hanno, F.A.C.P., Philadelphia, Pa., presented an address on "Internal Medical Problems in Ophthalmology" before the meeting of the Academy of Ophthalmology and Otolaryngology at Chicago on October 15, 1956.

Two Gold Heart Awards for outstanding contributions to the fight against heart disease and seven Howard W. Blakeslee Awards for distinguished reporting of advances in the field of heart and blood vessel disorders were presented on Oct. 28, 1956, by the American Heart Association. The awards were bestowed by Dr. Irvine H. Page, F.A.C.P., President, during the Association's Annual Dinner at the Netherland Hilton Hotel in Cincinnati, this being a highlight of the week-long Annual Meeting of that society.

Recipients of the Gold Heart Awards were Dr. Arlie R. Barnes, F.A.C.P., Rochester, Minn., and General Mark W. Clark (U. S. A., Ret.), President of The Citadel, the military college of South Carolina at Charleston. Dr. Barnes is a former President of the American Heart Association and General Clark has served as National Chairman of the Heart Fund Campaign during the past three years.

Dr. Paul D. White, M.A.C.P., Boston, Mass., was given a special Blakeslee Award for "creating better public understanding of heart disease through his press conferences, published articles, and radio and television appearances during the illness and recovery of President Eisenhower."

Dr. K. K. Chen, F.A.C.P., Indianapolis, Ind., a member of the U. S. National Committee for the International Union of Physiological Sciences, was appointed by the State Department one of the five official delegates to the First General Assembly at Brussels, Belgium, in connection with the XX International Physiological Congress.

At the October 16, 1956, meeting of the Michigan Rheumatism Society the following were elected as Officers for the coming year:

President—Dr. Dwight C. Ensign, F.A.C.P., Physician-in-Charge, Arthritis Division, Henry Ford Hospital, Detroit, Mich.

Vice President—Dr. Ivan F. Duff, F.A.C.P., Associate Professor of Internal Medicine in Charge of Rackham Arthritis Research Unit, University of Michigan Medical School, Ann Arbor, Mich.

Secretary-Treasurer—Dr. John W. Sigler, (Associate), Associate Physician, Arthritis Division, Henry Ford Hospital, Detroit, Mich.

Dr. Hobart A. Reimann, F.A.C.P., as guest of the Medical Association of Puerto Rico, gave lectures in San Juan, Ponce, and San Germán, Oct. 1–7, 1956.

Dr. Louis N. Katz, F.A.C.P., Chicago, Illinois, on October 27, 1956, was presented with the Albert Lasker Award of the American Heart Association "for distinguished achievement in the field of cardiovascular research." The award was conferred by Dr. Edgar V. Allen, F.A.C.P., Rochester, Minn., President-Elect of the American Heart Association. Dr. Katz was given the traditional statuette of the Winged Victory of Samothrace, symbolizing victory over death and disease, an honorarium of $1,000 and a scroll describing his accomplishments.

The Lasker Award for cardiovascular research was established by the Albert and Mary Lasker Foundation in 1953 in coöperation with the American Heart Association, through which it is presented.

Dr. James F. Hays, F.A.C.P., Medical Director of the International Latex Corporation, Dover, Delaware, attended the International Association of Industrial Medical Officers in London, England, September 24–28, 1956.

Dr. Esmond R. Long, M.A.C.P., Pedlar Mills, Virginia, was tendered an honorary luncheon at the Potts Memorial Institute, Hudson, New York, and was presented with a beautifully engrossed and leatherbound Citation reading as follows: "You have enriched every organization of which you have been a member and ennobled every task you have undertaken in the many fields relating to tuberculosis and allied problems, as scientific investigator, interpreter of research findings, editor, author, teacher, consultant and administrator. Your services in time of war to the United States Army, and in time of peace to our Veterans Administration, to the Department of Health, Education and Welfare and to the State Department, to our national universities and societies and to foreign governments have been so great that it has been truly said, 'No other living American has made so extensive a contribution to the control of tuberculosis.'"

Dr. J. S. Blumenthal, F.A.C.P., Associate Professor of Medicine and Chief of the Allergy Clinic, University of Minnesota, addressed the scientific meeting of the Ingham County Medical Society at Lansing, Michigan on October 16, 1956. His subject was "Some Newer Concepts in the Treatment of Allergy." On October 17, 1956, he addressed the Minnesota Academy of General Practice at St. Paul, and was moderator of a panel on allergy.

Any member wishing to present a paper at the Allergy Session of the American Medical Association Meeting at New York City in June, 1957, should write for suggestions for authors of section papers and standing rules of sections to the Secretary, Clarence Bernstein, M.D., 740 Magnolia Avenue, Orlando, Florida. Abstracts of papers, 250 words or less, will be accepted for possible inclusion in the program until January 15, 1957. Time and place will be announced at a later date.

Dr. Paul H. Morton, F.A.C.P., Coronado, Calif., presented a paper before the 57th General Meeting of Association of Clinical Pathologists in the Great Hall of the Royal College of the Surgeons of England, London, October 5, 1956, his paper dealing with the subject of the reticuloendothelioses.

Dr. Morton also presented a paper before the section on hematology of the Fourth International Congress on Internal Medicine at Madrid, Spain, September 21.

He also attended the Second European Congress on Cardiology held in Stockholm.

Dr. Lawrence E. Putnam, F.A.C.P., Washington, D. C., addressed a luncheon meeting of the Medical Staff of the Leland Memorial Hospital, Riverdale, Maryland, October 25, 1956, on "Reactions to Penicillin and Other Antibiotics." Dr. Putnam has recently resigned as Associate Medical Director of the Antibiotics Division of the Food and Drug Administration. He will continue in the practice of internal medicine.

A testimonial dinner was given by local Fellows and Associates of the College to Dr. Rafael Rodriguez-Molina, College Governor for Puerto Rico, on the occasion of the recent Puerto Rico Regional Meeting of the College at San Juan, Oct. 26–27, 1956. Dr. Rodriguez-Molina is serving his last year as the College Governor for Puerto Rico.

This was the sixth annual Regional Meeting of the College held in Puerto Rico. A scientific program was given in the auditorium of the Medical Society of Puerto Rico on Friday evening, Oct. 26, and at the University of Puerto Rico School of Medicine on Saturday afternoon, Oct. 27. A luncheon was tendered to the group at the University of Puerto Rico School of Medicine as a courtesy on behalf of the Dean of the Medical School Faculty, Dr. E. Harold Hinman, F.A.C.P.

Dr. Samuel J. Prigal, F.A.C.P., New York City, recently addressed the Section of Allergy and Infectious Diseases of the National Institutes of Health at Bethesda, Md., his subject being the "Interrelationship of Allergy and Infection."

On Sept. 4, 1956, the Karl Landsteiner Award of the American Association of Blood Banks was presented to Dr. Alexander S. Wiener, F.A.C.P., Senior Bacteriologist (Serology) to the Office of the Chief Medical Examiner of New York City, Assistant Professor of Forensic Medicine of New York University Post-Graduate Medical School, and Attending Immunohematologist of the Jewish Hospital of Brooklyn.

The citation was as follows:

"For valuable contributions to our knowledge of immunohematology and hemotherapy as they relate to blood banking, which has become an integral part of the art and science of medicine, and in particular for his rôle in the demonstration and identification of the rhesus and other red cell antigens and their relation to hemolytic transfusion reactions, the description of the behavior of Rh blocking antibodies, leading to the prevention of many hemolytic transfusion reactions.

"For developing the nomenclature of the Rh system and for advancing the theory of the heredity of the blood types and their application to clinical and forensic medicine, bringing honor to his teacher and friend, the late Dr. Karl Landsteiner, by helping to fulfill his prediction of red cell individuality."

Dr. Wiener is also Chairman of Subcommittees on Medicolegal Aspects of Blood Grouping and Blood Transfusion of the Committee on Medicolegal Problems of the American Medical Association. He participated in a postgraduate course in forensic pathology at the Armed Forces Institute of Pathology of the Walter Reed Army Medical Center in Washington, D. C., where on Oct. 31, 1956, he gave a lecture on

"Medicolegal Aspects of Blood Transfusion," which was followed by a discussion on general serologic methods.

Dr. Rudolph E. Fremont, F.A.C.P., Chief of the Cardiovascular Section of the Veterans Administration Hospital of Brooklyn, N. Y., on invitation by the First Pan American Congress on Gerontology and the National Institute of Cardiology of Mexico City, presented a paper on "Serious Cardiac Arrhythmias."

Dr. Howard T. Karsner, F.A.C.P., Medical Research Advisor to The Surgeon General of the Navy, has recently been elected a member of the New York Academy of Sciences.

Appointment to the National Advisory Heart Council of Dr. Howard P. Lewis, F.A.C.P., Regent of the American College of Physicians, and Professor of Medicine at the University of Oregon Medical School, Portland, Ore., was announced on Nov. 12, by the Surgeon General of the U. S. Department of Health, Education, and Welfare, Dr. Leroy E. Burney, F.A.C.P.

As a member of the National Advisory Heart Council, Dr. Lewis will make recommendation to the Surgeon General on programs of the National Heart Institute, established by Congress through the National Heart Act in 1948. This is one of seven National Institutes of Health at Bethesda, Md., main research arm of the Public Health Service.

Dr. Irving Graef, F.A.C.P., was recently honored by the National Committee for Resettlement of Foreign Physicians, New York City, as the retiring Chairman of the Board of Directors for his distinguished efforts in helping foreign physicians reëstablish themselves in their profession in the United States. Dr. Graef was presented with a bronze plaque and two volumes of letters of appreciation from members of the American community and the medical profession at a luncheon in his honor at the New York Academy of Medicine on Nov. 5, 1956.

A.C.P. Post-Convention Tour—1957

Following the 38th Annual Session of the American College of Physicians at Boston, April 8–12, 1957, a specially organized medical tour will be made to the Caribbean. All indications point to a large attendance. Briefly, the schedule includes special flight arrangements via Pan American World Airways direct from Boston, deluxe hotel accommodations, and sightseeing throughout. The schedule will be:

April 13: Boston to San Juan direct via Pan American.
14: Sightseeing, St. Thomas, Virgin Islands.
15: A.C.P. Scientific Program and Banquet.
16: Sightseeing, El Yunque Forest and Luquillo Beach.
17: Fly to Ciudad Trujillo. Hospital inspection.
18: Trip to Boca Chica and Isle of Matica.
19: Port-au-Prince, Sightseeing and Reception.
20: Trip to Albert Schweitzer Memorial Hospital.
Evening sailing SS CRISTOBAL.
21: Departure for New York or Miami by air.
24: SS CRISTOBAL arrives New York.

Note the change in the sailing date from Port-au-Prince and a corresponding reduction in cost for those desiring the air/sea combination:

Air/Sea, including land arrangements	$426.20
Air return to New York, including land arrangements	$409.00
Air return to Miami, including land arrangements	$355.00

A well integrated program of sightseeing and entertainment has been arranged, as well as medical programs in San Juan, the Dominican Republic, and Haiti. The program is at press, and will be distributed to all members interested. Inasmuch as this is a medical tour, expenses of the doctors should be tax-deductible.

If the return is by air to either Miami or New York, stopovers are permitted at Montego Bay or Kingston in Jamaica, and Havana, Cuba, with no increase in the transportation cost.

Early communications and inquiries should be sent immediately to Mr. Joseph P. Sims, Jr., The House of Travel, 1600 Walnut St., Philadelphia 3, Pa., who will be the Tour Conductor. A deposit of $75.00 per person, refundable in the event of cancellation, is required to hold reservations definite.

OBITUARIES

RECENT DEATHS OF A.C.P. MEMBERS

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

Dr. William Pope Baker, F.A.C.P., Atlanta, Ga., July 11, 1956
Dr. Samuel Sylvester Berger, F.A.C.P., Cleveland, Ohio, Sept. 18, 1956
Col. Charles Kettig Berle, (MC), USA, Ret'd., F.A.C.P., San Francisco, Calif., Sept. 13, 1956
Dr. Robert Warren Blumenthal, F.A.C.P., Milwaukee, Wis., July 1, 1956
Dr. Daniel Parsons Foster, F.A.C.P., Detroit, Mich., August 21, 1956
Dr. Julian Erdreich Meyer, F.A.C.P., Columbus, Nebr., Oct. 5, 1956
Dr. Louis Harry Newburgh, F.A.C.P., Valley Center, Calif., July 17, 1956
Dr. Charles Edwin Sears, F.A.C.P., Portland, Ore., Oct. 4, 1956
Dr. John William Shuman, Sr., F.A.C.P., Santa Monica, Calif., August 4, 1956
Dr. Charles William Warren, F.A.C.P., Rochester, N. Y., Nov. 4, 1956

The College headquarters at 4200 Pine St., Philadelphia 4, Pa., would appreciate it if members and readers send in notices of the deaths of members promptly, so that suitable obituaries may be prepared and published. Frequently, deaths of members are not reported for several weeks or even months after a member is deceased.

DR. ORVILLE EVERETT BARBOUR

Dr. Orville E. Barbour, a prominent Peoria pediatrician, died at his home on October 12, 1956, of chronic rheumatic heart disease and pulmonary embolism. He was born at Indianapolis, Indiana, on June 25, 1893.

Dr. Barbour graduated from Bradley Institute in 1914 and received his M.D. Degree from St. Louis University School of Medicine in 1919. He interned at St. Louis City and Milwaukee County Hospitals following which he took postgraduate work at the New York Postgraduate Hospital and St. Louis Children's Hospital, completing this education in 1921.

Dr. Barbour was a member of the Staff of Methodist Hospital since 1920, was a past president of the Peoria Medical Society, and past president of the Pediatric Section of the Pan-American Medical Association. He organized the premature infant center at St. Francis Hospital, Peoria. He served as a member of the board of the South Side Mission and had been pediatrician at the Florence Crittenden Home and The Neighborhood House.

Dr. Barbour was a diplomate of the American Board of Pediatrics, and he held membership in the following organizations: Fellow, American College of Physicians (1930); Peoria County Medical Society; Illinois State Medical Society; American Medical Association; American Association for the Advancement of Science; American Academy of Pediatrics; Chicago Pediatric Society; and the American Editors and Authors Association.

In addition to his heavy professional schedule, Dr. Barbour was very active in civic and fraternal work. His death is deeply regretted by his numerous friends. He is survived by his wife and three daughters of 3807 North Evergreen Street, Peoria, Illinois.

CHARLES H. DRENCKHAHN, M.D., F.A.C.P.,
Governor for Southern Illinois

DR. ARTHUR CARLISLE CHRISTIE

The death of Dr. Arthur C. Christie on June 22, 1956, brought to a close a notable career in radiology covering some forty years and exerting an incalculable influence upon that specialty.

Arthur C. Christie was born in West Sunbury, Pa., December 29, 1879, the son of Dr. Milton Christie and Harriet Rhodes Christie. His father was a country physician so that his association with medicine was life long. After his early education in the public schools of Corry, Pa., he took his medical degree from the Cleveland College of Physicians and Surgeons (now incorporated in Western Reserve University School of Medicine). Following this he practiced medicine in Clymer, N. Y., for a short time, then entered the Medical Corps of the United States Army, being commissioned a First Lieutenant in 1907. His active duty included tours in the Philippines and various posts in this country where, at Columbus Barracks, Columbus, Ohio, he first became interested in radiology; his final duty in the Army was as Professor of Roentgenology and Operative Surgery at the Army Medical School, 1912–1916, at which time he resigned to enter the private practice of radiology. In 1917 he was appointed Chief of the Division of Roentgenology of the Medical Department of the Army, and organized this new unit entirely with Reserve personnel. In 1918, he was commissioned Colonel and made Chief Consultant in Radiology and served in this capacity with the A.E.F. in France from October 1918 to February 1919. Following this he returned to civilian practice in association with Dr. Thomas R. Groover, and Dr. Edwin A. Merritt (both of whom predeceased him), an association which continued many years until the earlier decease of both.

Over the years of study and teaching he developed great ability as a radiologist, and became nationally and internationally recognized in his field, being President of the 5th International Congress of Radiology in 1937, and an Honorary Fellow of the Faculty of Radiologists of Great Britain, among other international honors.

He achieved many other professional distinctions, local and national, and was always willing to work vigorously for good causes, whether professional or extra professional. For a long period he was Professor of Roentgenology at George Washington University School of Medicine, and also Professor of Clinical Radiology at Georgetown University Medical School. Throughout his medical life he contributed frequently to the literature and, in addition, was Editor of the American Journal of Roentgenology and Radium Therapy from 1924–1929. He had been a Fellow of the American College of Physicians since 1923.

As one of his close associates has written, "He contributed freely of his time as teacher, consultant, and adviser, and, because of his warm, kindly, and thoughtful nature, old and young looked to him for advice concerning their personal careers and problems."

In addition to his professional activities he had a deep interest in religion, and for many years taught a bible class every Sunday morning.

He was a warm and kindly friend, a man whom "it was good to see"—always courteous and interested in others—doing, without any show, innumerable kind and generous acts for those in need.

He leaves a distinguished name and a host of friends who loved and admired him. Our profession is poorer for his going.

John Minor, M.D., F.A.C.P.,
Governor for the District of Columbia

DR. ERNEST H. FALCONER

Dr. Ernest H. Falconer, LL.D., F.A.C.P., former Governor, Regent, and First Vice President of the American College of Physicians, died August 11, 1956, at his summer home in Los Gatos, California, of acute diverticulitis of the colon with peritonitis.

Dr. Falconer was born in Pardeeville, Wisconsin, on May 19, 1883. He received his medical degree cum laude as final prize man for highest standing at McGill University Medical School in 1911. After three years postgraduate training at the Montreal General Hospital and the Lake Edward Sanitarium in Quebec, Dr. Falconer came to the University of California Hospital in San Francisco as the first resident in medicine under the late Herbert C. Moffitt, Sr., from 1914 until 1916.

During the first World War Dr. Falconer was on the medical service of Base Hospital No. 30, the University of California affiliated unit in France, and following the war returned to the University of California Medical School as assistant clinical professor. In 1921 he established the hematology clinic at the University of California Hospital and became associate professor of medicine in 1923, and clinical professor of medicine in 1931.

Early in his professional career, Dr. Falconer became active in the affairs of the American College of Physicians and devoted much time throughout the remainder of his life to the College. He became a Fellow in 1928, and in 1936 was elected Governor for Northern California, which position he held until he was appointed to the Board of Regents in 1947. He was a Regent until 1950 at which time he was elected First Vice President.

During World War II Dr. Falconer was chairman of the committee appointed by the American College of Physicians, the American College of Surgeons and the A.M.A. to organize and supervise postgraduate clinics and lectures for military hospitals throughout Northern California. In 1948 he served with Dr. William J. Kerr as co-chairman of the annual meeting of the American College of Physicians in San Francisco.

Dr. Falconer was not only active in the official circles of the College but was continuously active in encouraging promising young internists to become associated with the College, and he always urged members to attend meetings. He frequently attended meetings with younger members and saw to it that they got the most out of the meetings, both in the lecture halls and in the social gatherings after hours. Many of his old friends will recall his great delight in story telling which he had developed to a fine art.

McGill University ranked very high in Dr. Falconer's interest. For many years he interviewed all applicants from the Northern California area for its medical school. Later he helped organize the McGill Society of Northern California, and was elected Regional Vice President of the McGill Graduate Society in 1947. On May 27, 1953, McGill University conferred an Honorary LL.D. for Dr. Falconer's services to medicine and to McGill University, and in 1954 he was made an Honorary Life Member of the McGill Graduate Society.

Since the first World War Dr. Falconer practiced the specialty of internal medicine in San Francisco and became widely known as a consultant in hematology. Throughout his career he was especially interested in the study of hematology and had published 35 papers on various aspects of this subject. Many of these papers have been presented at American College of Physicians' meetings, and were published in the ANNALS OF INTERNAL MEDICINE. These published papers represent only a small portion of the work done by Dr. Falconer in this field. Much of his work has been a great stimulus to students, many of whom have gone on to become leaders in the field of hematology.

In addition to his professional career Dr. Falconer was a great out-of-door enthusiast and spent much time hiking, fishing and swimming, and was a familiar figure striding over the Marin County trails near San Francisco.

To all those who knew Ernest Falconer the following quotation from the biography of Sir Walter Scott fits him well:

> "His sunny genial nature, his unfailing kindness, the simplicity with which he bore his honors, made him one of the most attractive figures."

Dr. Falconer is survived by his widow, Ruth Scott Falconer, 2705 Larkin Street, San Francisco, California.

JAMES H. THOMPSON, M.D., F.A.C.P.

DR. LOUIS GREENWALD

Dr. Louis Greenwald, F.A.C.P., died on August 27, 1956 in New York City of myocardial infarction.

Dr. Greenwald was born in Hungary, September 10, 1888. He became a naturalized U. S. citizen in 1904. He attended the College of the City of New York and received his degree of Doctor of Medicine in 1911 at New York University Medical College.

His hospital appointments were as follows: Clinical Instructor in Medicine at New York Medical College, Flower and Fifth Avenue Hospital in 1937 and he successively moved up to Associate Clinical Professor of Medicine. He served on the staffs of Beth Israel Hospital, Good Samaritan Hospital, Columbus Hospital, and Metropolitan Hospital. His last appointments were Consulting Physician, Metropolitan Hospital and Consultant in Hematology, Prospect Heights Hospital (Brooklyn).

He was a Diplomate of the American Board of Internal Medicine; member of the Eastside Clinical Society, New York Academy of Sciences, New York County Medical Society, New York State Medical Association, American Medical Association, and the Society for the Study of Blood. He entered the American College of Physicians as an Associate in 1947 and became a Fellow in 1951. He is the author of numerous publications in leading medical journals.

He is survived by his widow, Mrs. Rebecca Greenwald, 99 E. 4th Street, New York City, and three children. It is with sincere regret that his loss is recorded.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. CASSIUS HOWARD HOFRICHTER

Dr. Cassius Howard Hofrichter, F.A.C.P., of Seattle, Washington, died on October 3, 1956. He was born in Cleveland, Ohio, August 6, 1891. He was graduated from Hiram College with the A.B. Degree in 1916 and from Western Reserve University School of Medicine with the degree of Doctor of Medicine in 1919. He served in the Army Medical Corps during World War I.

From 1920 to 1921 he was Associate Professor of Physiology at the University of West Virginia. Subsequently, he moved to Seattle where he practiced internal medicine for many years. In 1927, he did postgraduate work at the University of Vienna. He was a member of the King County Medical Society, the Washington State Medical Association and the American Medical Association. He was past president of the Washington State Diabetes Association, past president of the Seattle Academy of Internal Medicine. He became a member of the American Congress of Internal Medicine in 1921, an Associate of the American College of Physi-

cians in 1926 and a Fellow of the College in 1937. Dr. Hofrichter was a member of the Board of Trustees of the Seattle General Hospital and Consultant in Diabetes to the Children's Orthopedic Hospital of Seattle. He was also a member of the staff of the King County Hospital in Seattle.

Some years prior to his death, he retired from active practice and served as Medical Director for the Northern Life Insurance Company of Seattle.

He is survived by his widow, Mrs. Gertrude Pratt Hofrichter, 9749 N. E. Fifth Street, Bellevue, Washington.

JAMES W. HAVILAND, M.D., F.A.C.P.,
Governor for Washington

DR. LEGRAND KERR

Dr. LeGrand Kerr died on August 10, 1956 at Sayville, New York, of a cerebral hemorrhage.

Dr. Kerr was born May 11, 1870. He received his degree of Doctor of Medicine in 1892 at Bellevue Hospital Medical College.

He was Consulting Pediatrician of the Brooklyn Society for the Prevention of Cruelty to Children, Rockaway Beach Hospital and Dispensary, Williamsburgh Maternity Hospital, Bushwick Hospital, Swedish Hospital, and Methodist Episcopal Hospital.

He was a Diplomate of the American Board of Pediatrics; Fellow, American Academy of Pediatrics and a Charter Fellow of the American College of Physicians since 1916.

He is survived by his widow, Mrs. Edith May Kerr, 311 Candee Avenue, Sayville, Long Island, New York. It is with regret that the end of his long and useful life is noted.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. CHARLES WESLEY LAYNE

Dr. Charles W. Layne, F.A.C.P., died on September 21, 1956, at Newburgh, New York, of hepato-renal failure secondary to the development of a cast involving practically the entire biliary tract.

Dr. Layne was born in Fairview, Kentucky, on November 16, 1900. He received his degree of Doctor of Medicine in 1928 at Emory University School of Medicine, Atlanta, Georgia.

He was an intern at Bellevue Hospital in 1929–30. He did postgraduate study on the Alexander Cochran Bowen Foreign Scholarship in 1931–32. His practice was limited to Internal Medicine.

His hospital appointments were as follows: Consulting Physician, Harlem Valley State (Wingdale) and Matteawan State (Beacon) Hospitals; Consulting Physician, Craig House (Beacon); and was on the staff of St. Luke's Hospital since 1933.

He was a diplomate of the American Board of Internal Medicine; member of the Orange County Medical Society, New York State Medical Society, American Medical Association, New York Academy of Medicine, American Heart Association, and Fellow of the American College of Physicians since 1944.

He is survived by his widow, Mrs. Ada Layne of 403 Grand Street, Newburgh, New York. His confreres note with sincere regret the passing of Dr. Layne.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. BENJAMIN MARKOWITZ

Dr. Benjamin Markowitz, F.A.C.P., died on September 17, 1956, at Bloomington, Illinois, after a chronic illness. He was born August 14, 1896, at Pottstown, Pennsylvania. He attended Bucknell University from 1915–17, and Loyola University of Chicago where he received his B.S. degree. He received his M.D. degree from Loyola University School of Medicine in 1922. Following graduation he interned at Swedish Convenant Hospital, Chicago. He took his postgraduate work in Pathology at Cook County Hospital, Chicago, from 1927–30, following which he located at Bloomington. Dr. Markowitz was pathologist for many years for the following hospitals—Mennonite and St. Joseph's of Bloomington; Brokaw of Normal, Illinois; Abraham Lincoln and St. Clara's of Lincoln, Illinois, and for a time was visiting pathologist for Burnham City Hospital and Mercy Hospital, both of Champaign, Illinois.

He was a Fellow of the American College of Physicians since 1943. He was a Diplomate, American Board of Pathology. In addition to membership in the local, state and national (A.M.A.) medical societies, he was a member of the Illinois State Pathological Society, the American Society of Clinical Pathologists, and the American College of Pathologists. He was a former Health Director of Bloomington. Dr. Markowitz attended many of the postgraduate courses and regional meetings of the College and was author of many publications appearing in State and National Medical Journals.

Dr. Markowitz was well known and respected by his contemporaries and by the public. He is survived by his wife, Mrs. B. Markowitz of 500 Patterson Drive, Bloomington, Illinois, and two children.

CHARLES H. DRENCKHAHN, M.D., F.A.C.P.,
Governor for Southern Illinois

DR. MICHAEL ALEXANDER OGDEN

After a series of minor cerebral accidents, Dr. Michael Alexander Ogden, F.A.C.P., died on September 13, 1956. He was born in Russia on December 24, 1892, under the name of Maxim Alexander Oginsky. He received his early education in Russia and obtained his medical degree in 1918 from the Imperial Novorossiski University of Odessa. During the Bolshevik Revolution, he fled the country and sought asylum in the United States where he became a naturalized citizen and changed his name.

Dr. Ogden specialized in Clinical Pathology and Hematology. He was at one time Director of the Laboratory and Pathologist at Passaic General Hospital but, in recent years, he operated a private laboratory. He was a Diplomate, American Board of Pathology, and author of a number of publications in his field. He was elected a Fellow of the American College of Physicians in 1932.

He is survived by his widow who came to this country with him from Russia.

EDWARD C. KLEIN, JR., M.D., F.A.C.P.,
Governor for New Jersey

DR. CORNELIUS C. PERRINE

Dr. Cornelius C. Perrine, F.A.C.P., died suddenly at his home in Fair Haven, N. J., on June 22, 1956, of coronary occlusion. He was born on March 9, 1906, received his A.B. in 1928 from Rutgers University and his M.D. in 1932 from Jefferson Medical College of Philadelphia.

Following his internship at Cooper Hospital in Camden, he started practice in his home community where he attained the esteem and affection of his colleagues and patients. He pursued numerous, short, postgraduate courses over the years, many of which were organized by the American College of Physicians.

He was attending physician in medicine at Monmouth Memorial Hospital in Long Branch; attending physician and Director of Service, Riverview Hospital in Red Bank. He was former President of Monmouth County Heart Association; member of Monmouth County Medical Society, Medical Society of New Jersey, the American Medical Association, New Jersey Heart Association and American Heart Association. He was a Diplomate of the American Board of Internal Medicine. He was elected an Associate of the College in 1942 and he was advanced to Fellowship in 1950.

During World War II, Dr. Perrine served with distinction in the Naval Reserve Medical Corps. Always active in attending the meetings of the College, he also was an interested participant in the civic and medical problems of his area and state.

Dr. Perrine's death, at the early age of 50, was a shock to his many friends and a real loss to his community. He will be sorely missed by his colleagues who affectionately knew him as a great raconteur, a golfer and a craftsman in woodwork.

He is survived by his wife, Mrs. Dorothy B. Perrine; his daughters, Mrs. Shirley P. Maggi and Miss Constance M. Perrine; his son, Robert G. Perrine, and his mother, Mrs. Eva Perrine.

EDWARD C. KLEIN, JR., M.D., F.A.C.P.,
Governor for New Jersey

DR. NELSON GORHAM RUSSELL, SR.

Nelson Gorham Russell, Sr., a Fellow of the American College of Physicians since 1922, and Governor for Western New York from 1938 to 1946 was born in Newmarket, Ontario, August 26, 1872. He was the son of Dr. Stephen A. and Helena Hackett Russell and his grandfather, also a physician, had treated the Osler family who lived four miles from Newmarket. Dr. Russell's early education was in Canadian public schools. In after years he frequently referred to the thorough training he received. For a time his seatmate was Walter A. Bastedo, F.A.C.P., who became professor of pharmacology at Columbia. The Russell family came to New York State and Dr. Russell entered the Medical School of the University of Buffalo from which he graduated in 1895. After his internship at the Buffalo General Hospital he did postgraduate work in Europe, including London, Berlin, and Vienna.

Returning to Buffalo, he became an assistant in pathology and later assistant in medicine at the Medical School of the University of Buffalo and at the Buffalo General Hospital. For years he continued to do autopsies at the General and other hospitals in addition to the teaching of medicine and a busy private practice. Promotions followed successively until he became clinical professor of medicine in 1923 and professor of medicine and head of the department in 1929. Reaching his sixty-fifth birthday in 1937, he was named professor of medicine emeritus.

He entered military service in 1917 as head of medicine in Base Hospital 23 sponsored by the Buffalo General Hospital. After some months of service with his outfit at Vittel, France, he was promoted to be Chief Consultant to Base Section Two with headquarters at Bordeaux. He had over 30 hospitals under his supervision with more than 30,000 patients, and he covered 1100 miles on his round of hospitals. In 1918 Dr. Russell received a citation from General Pershing for "exceptionally meritorious and conspicuous service." After the war he was retired to civilian life with the rank of colonel.

He was attending physician and chief of the medical service at the Buffalo General Hospital and consultant at several other hospitals. He was a member of the Board of Trustees of the General Hospital and vice president of the Board for a number of years.

He was most civic-minded and gave a great deal of his time, thought and effort to the needs of the community. As a young physician he recognized the plight of the children of the indigent and he personally founded the milk dispensaries which became the well-baby clinics of Buffalo.

Dr. Russell was called to public service in Buffalo three times. He was a member of the Board of Health of the City and later was made chairman of the Advisory Health Board. In 1944 he was made chairman of the Board of Managers of the Meyer Memorial Hospital, at that time the municipal hospital. In each of the latter two instances Dr. Russell was called upon as a non-partisan, non-political figure highly respected in the community, in order to settle political situations which had enveloped each of those bodies. Each time Dr. Russell accepted the assignment and removed public health from politics.

He was for years a director of the Buffalo Philharmonic Orchestra Society and a regular attendant at the concerts. He was a director also of the Albright Art Gallery and of the Nichols School. He was a former Dean of the Saturn Club. His medical affiliations were numerous and distinguished. They included the American College of Physicians, the Medical Society of the County of Erie, the Medical Society of the State of New York, the American Medical Association, the American Association of Pathologists and Bacteriologists, the American Clinical and Climatological Association, the American Heart Association, the American Association of the History of Medicine, the American Trudeau Society, the Society of Experimental Biology and Medicine, the Buffalo Academy of Medicine, and Alpha Omega Alpha. He was certified by the American Board of Internal Medicine.

For 28 years he served as an alumni member of the Council (Board of Trustees) of the University of Buffalo and for a number of years on its general administration (executive) committee. On February 22, 1945, the University conferred on him its highest honor, the Chancellor's Medal, "in recognition of a lifetime of eminent service to your profession, your community and your country."

For years a vestryman and senior warden of All Saints Episcopal Church, in 1951 he was presented by the Bishop of the Diocese with the Bishop's Cross and was named Layman of the Year.

His devotion to his patients was remarkable. When he was past 80, he was known to have gone out after midnight to see some friend in dire distress. A man of few words, he was imbued with a devastating wit—laconic but quick and keen. Chancellor Capen, of the University of Buffalo, said of him that he had become a legend in his lifetime.

The Council of the University recorded in its minutes: "Hundreds of young men and women who studied medicine under his guidance have had their lives quickened by the sharp encounter with his fine, precise mind, encouraged by the gentle human qualities of the man who was never too occupied to listen to their problems, and endlessly enriched by the experiences of his friendship. In his profession he was acknowledged generally as a leader among physicians and a master diagnostician. To the art of healing and to the science of medicine he brought a high degree of learning, rare insight and accuracy of judgment and the highest degree of integrity."

His associates at the medical school have suggested for his memorial the words of Dr. John Finley:

"Sought by the greatest and the least as friend
He gave himself unsparingly to the end.
He even kept Death waiting at the door
'Til he could do a friend one kindness more."

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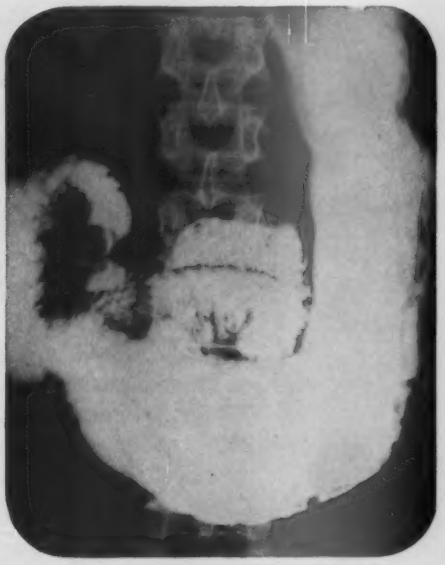
DIAGNOSTIC AID

Reduced Hypermotility with Pro-Banthine® Improves Visualization

*Posterior-anterior film: definite hyperperistalsis with poor duodenal visualization.**



Posterior-anterior film after 15 mg. of Pro-Banthine intramuscularly: chronic duodenal ulceration clearly disclosed.

The same anticholinergic action which has made Pro-Banthine (brand of propantheline bromide) the outstanding therapeutic agent in peptic ulcer has also proved valuable in diagnosis.

By controlling the hypermotility, Pro-Banthine may permit delineation of a lesion otherwise not clearly visualized.

The technic is simple: If the first set of films shows hypermotility but no filling defect is demonstrable, reexamination is done a few minutes after intramuscular injection of 15 mg. or a half hour after oral administration of 30 mg. of Pro-Banthine.

This procedure has the additional advantage of demonstrating the patient's response to a given dosage of the drug.

G. D. Searle & Co., Chicago 80, Illinois, Research in the Service of Medicine.

*Roentgenograms courtesy of I. Richard Schwartz, M.D., Kings County Gastrointestinal Clinic, Brooklyn, N.Y.

SEARLE

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A Better Antihypertensive

. . . because among all Rauwolfia preparations Rauwiloid (alseroxylon) is maximally effective and maximally safe . . . because least dosage adjustment is necessary . . . because the incidence of depression is less . . . because up to 80% of patients with mild labile hypertension and many with more severe forms respond to Rauwiloid alone.

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. . . because Rauwiloid's *nonsoporific* sedative action relieves anxiety in a long list of unrelated diseases not necessarily associated with hypertension . . . without masking of symptoms . . . without impairing intellectual or psychomotor efficiency.

Dosage: Simply two 2 mg. tablets at bedtime. After full effect one tablet suffices.

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In moderate to severe hypertension this single-tablet combination permits long-term therapy with dependably stable response. Each tablet contains 1 mg. Rauwiloid and 3 mg. Veriloid. Initial dose, 1 tablet t.i.d., p.c.

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In severe, otherwise intractable hypertension this single-tablet combination provides smoother, less erratic response to hexamethonium. Each tablet contains 1 mg. Rauwiloid and 250 mg. hexamethonium chloride dihydrate. Initial dose, ½ tablet q.i.d.

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Toxicity is minimal—no case of liver damage has been reported.
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between the hazards of high steroid dosage
and the frustration of inadequate relief

Because of the complementary action of cortisone and the salicylates, Salcort produces a greater therapeutic response with lower dosage.

One study concludes: "Salicylate potentiates the greatly reduced amount of cortisone present so that its full effect is brought out without evoking undesirable side reactions."[1]

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indications:

Rheumatoid arthritis . . . Rheumatoid spondylitis . . . Rheumatic fever . . . Neuromuscular affections.

[1]Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. *11*:1105.

each tablet contains:

Cortisone acetate	2.5 mg.
Sodium salicylate	0.3 Gm.
Aluminum hydroxide gel, dried	0.12 Gm.
Calcium ascorbate (equivalent to 50 mg. ascorbic acid)	60.0 mg.
Calcium carbonate	60.0 mg.

**U.S. Pat. 2,691,662*

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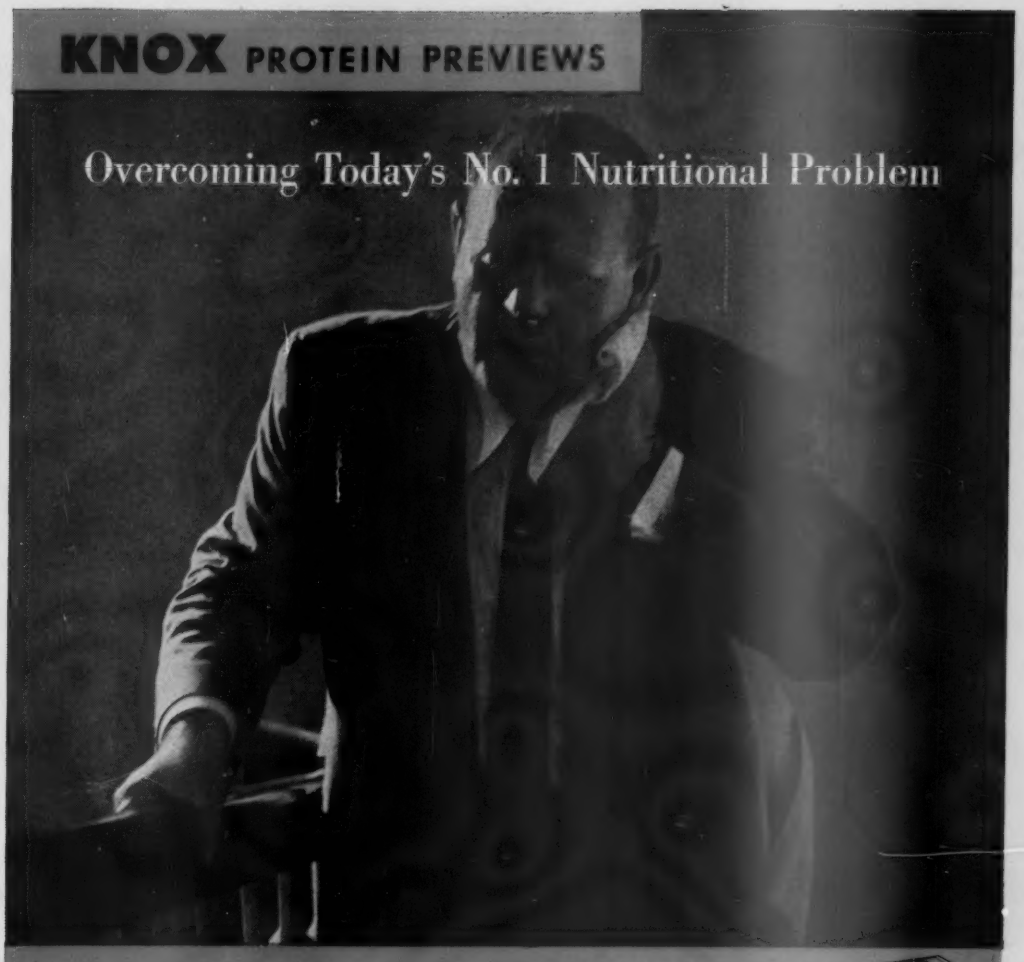

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1. Color-coded diets of 1200, 1600 and 1800 calories are based on nutritionally-sound Food Exchanges.[1]

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3. Diets promote accurate adjustment of caloric levels to the special needs of the patient yet allow each individual considerable latitude in the choice of foods.

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1. The Food Exchange Lists referred to are based on material in "Meal Planning with Exchange Lists" prepared by Committees of the American Diabetes Association, Inc., and The American Dietetic Association in cooperation with the Chronic Disease Program, Public Health Service, Department of Health, Education and Welfare.

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Please send me ..... dozen copies of the new illustrated Knox Reducing booklet based on Food Exchanges.

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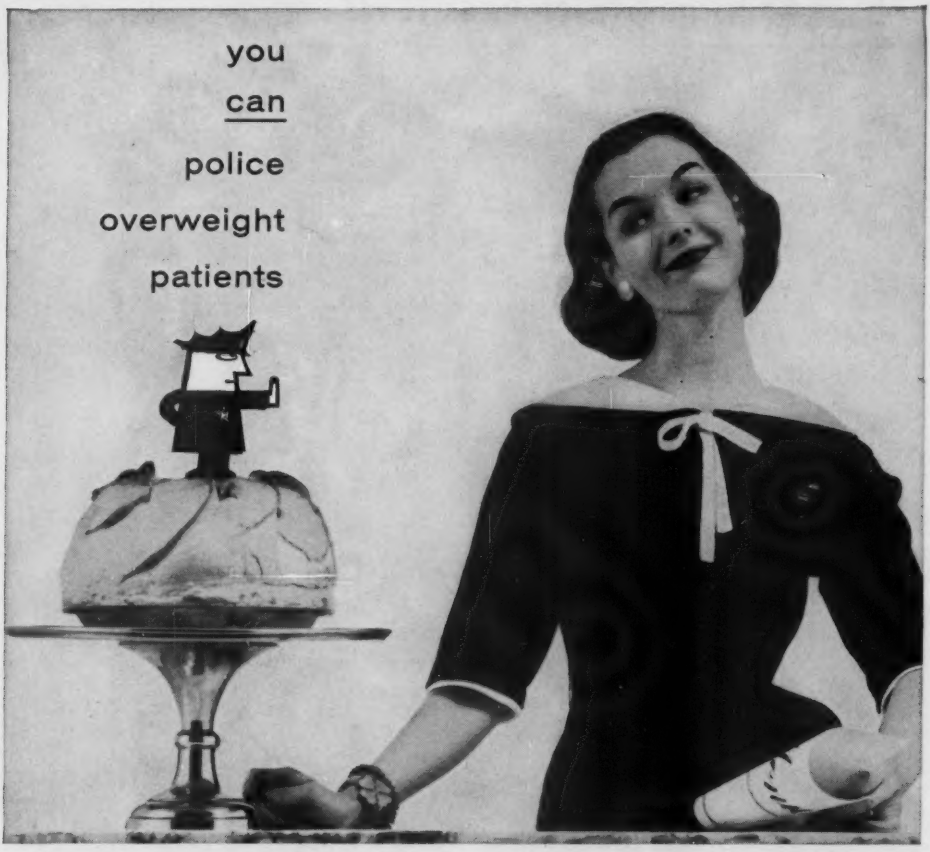

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Hunger contractions as well as subjective feelings of hunger are effectively diminished by REVICAPS.

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measure of time—and that is the *background* of the
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"...dioctyl sodium sulfosuccinate [Doxinate] results in restoration of normal function both in terms of stool consistency and frequency."

—CASS, L.J., AND FREDERIK, W.S.: AM. J. GASTROENTEROL. (DEC.) 1956.

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—FRIEDMAN, M.: AM. PRACT. & DIGEST OF TREATMENT (OCT.) 1956.

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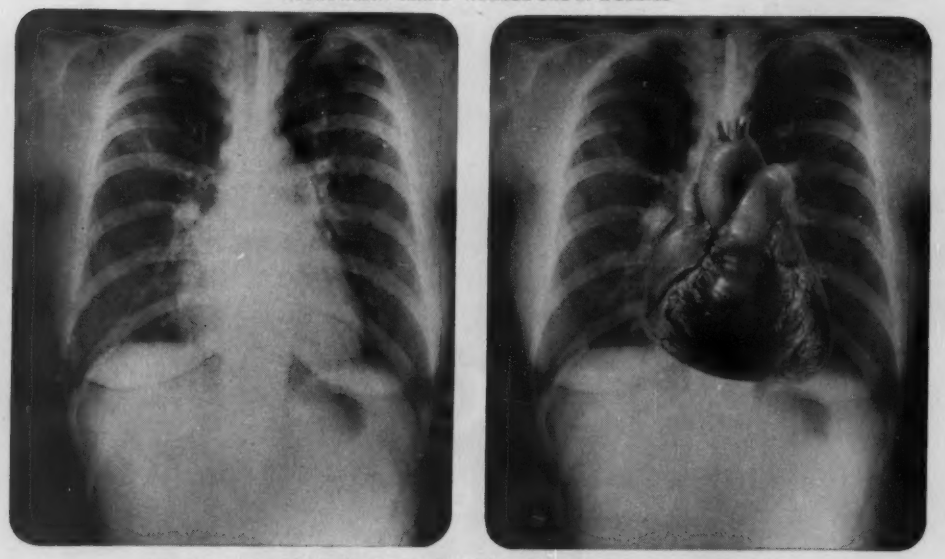

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ROENTGEN CONFIGURATION—Postero-anterior examination—moderate heart enlargement—right ventricular enlargement—prominence of pulmonary artery segment.

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*EHRLICH, J.C.: ARIZONA MED. 12:239 (JUNE) 1955. BIBLIOGRAPHY FURNISHED ON REQUEST

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*Reifenstein, E. C., Jr., in Harrison, T. R.: Principles of Internal Medicine, ed. 2, New York, The Blakiston Company, Inc., 1954, chap. 98, pp. 702, 703.

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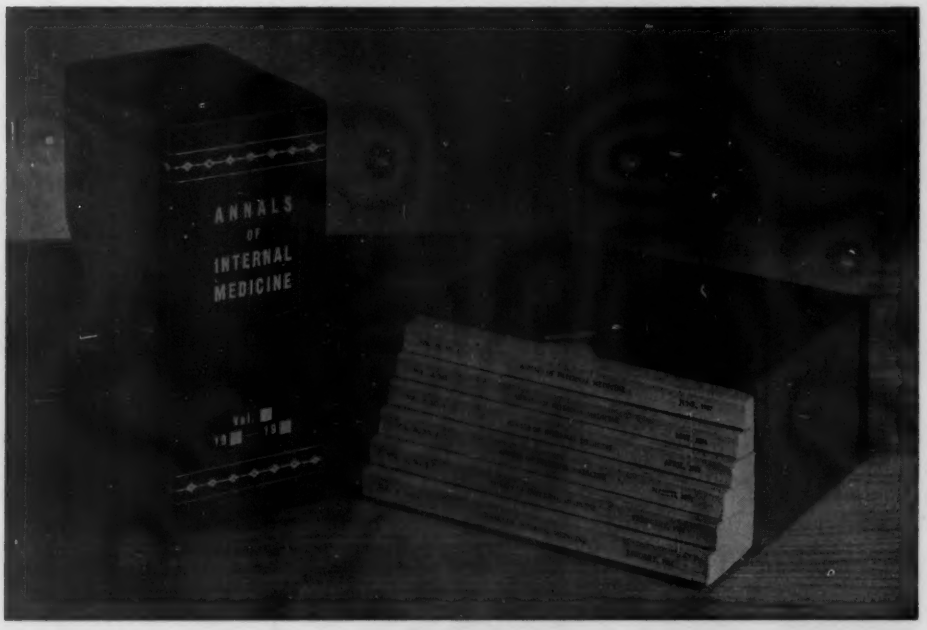

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Supplied:

Gel — 12 oz. bottles. Tablets — bottles of 100 and 1,000.

1. Johnston, R.L.: J. Indiana St. M.A. 46:869, 1953. 2. McHardy, G., and Browne, D.: Southern M. J. 45:1139, 1952.

*Merrell's distinctive antispasmodic that is more effective than atropine—free from side effects of atropine.[2]

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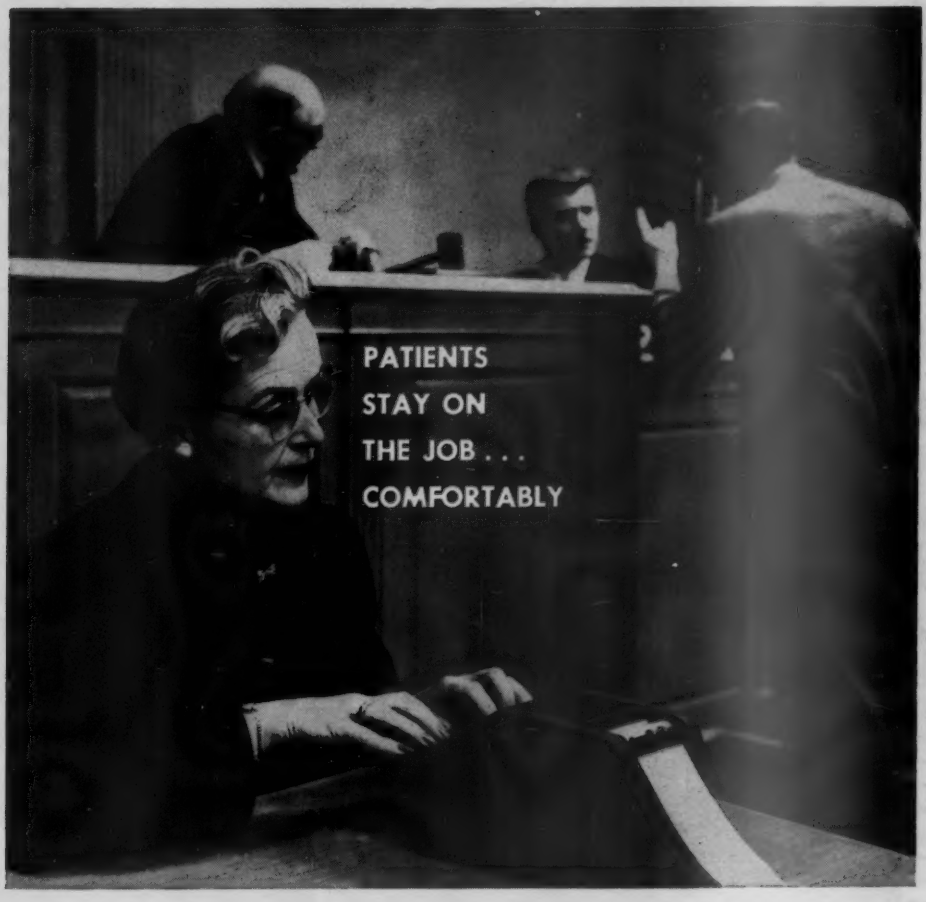

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1. Martin, W. J., et al.: J.A.M.A. *160*:925 (March 17) 1956.

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shock
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1. Binder, M. J., et al.: **Am. Jour. Med.**, 18:622, Apr., 1955. **2.** Sampson, J. J.; and Zipser, Albert: **Circulation**, 9:38, Jan., 1954. **3.** Nichol, E. S., in Conn, H. F.: Current Therapy 1954. Philadelphia, W. B. Saunders Co., 1954, p. 196. **4.** Jamison, W. L., et al.: **Jour. Am. Geriat. Soc.**, 3:521, Aug., 1955. **5.** Gilchrist, A. Rae: **Brit. Med. Jour.**, 2:351, Aug. 16, 1952.

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as manifested by coronary-artery disease and its relationship to atherosclerosis

New Findings Related to the Disease

A report[1] by a joint group of eminent researchers ". . . establishes clearly for the first time that elevation of blood lipids *precedes* clinical coronary disease and predicts it. . . ." This cooperative study shows that atherosclerosis is clinically manifested by a prior elevation of total cholesterol and S_f 20-100 lipoproteins. According to the report, the most practical method for measuring the elevation is by the total cholesterol measurement.

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1. Joint Report of the Technical Group of the Committee on Lipoproteins and Atherosclerosis (Gofman, J.W., et al.) and the Committee on Lipoproteins and Atherosclerosis of the National Advisory Heart Council (Andrus, E.C., et al.): Circulation *14*:691 (Oct.) 1956.
2. Sherber, D.A.: Paper read before the Meeting of the Michigan Academy of General Practice, Detroit, Nov. 7, 1956.
3. Sherber, D.A., and Levites, M.M.: J.A.M.A. *152*:682 (June 20) 1953.
4. Sherber, D.A., et al.: To be published.
5. Fuller, H.L.: Personal communications.
6. Bordin, C.: Personal communications.
7. Albert, A., and Albert, H.: Texas State J. Med. *50*:815 (Dec.) 1954.

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1. Personal communication to S.K.F.

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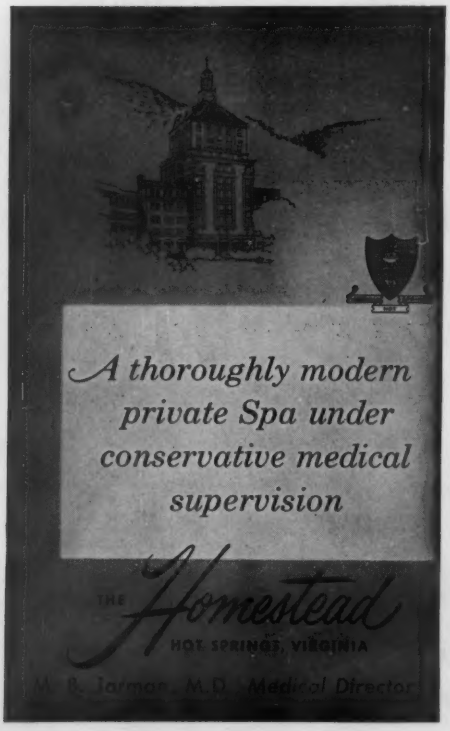
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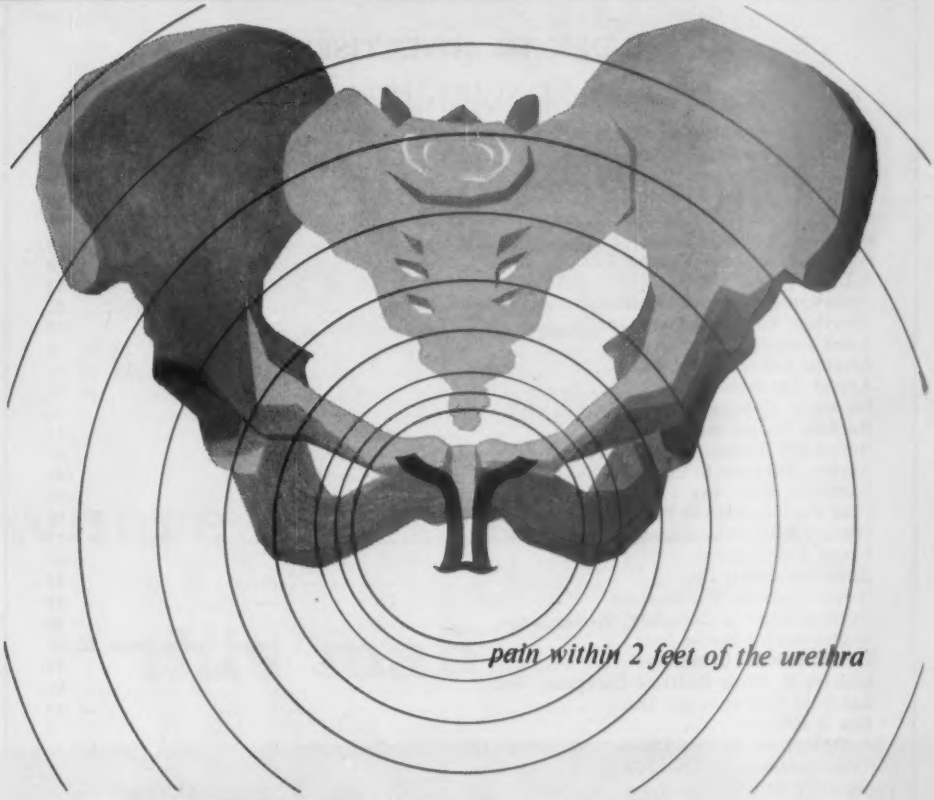

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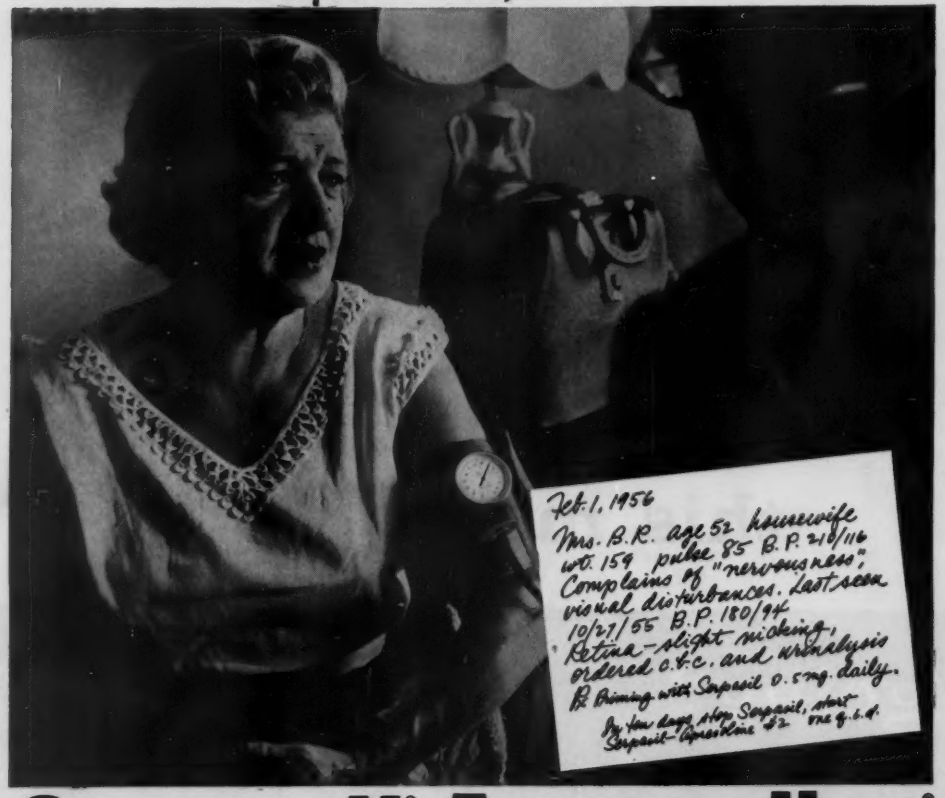
when blood pressure must come down


Feb. 1, 1956
Mrs. B.R. age 52 housewife
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(reserpine and hydralazine hydrochloride CIBA)

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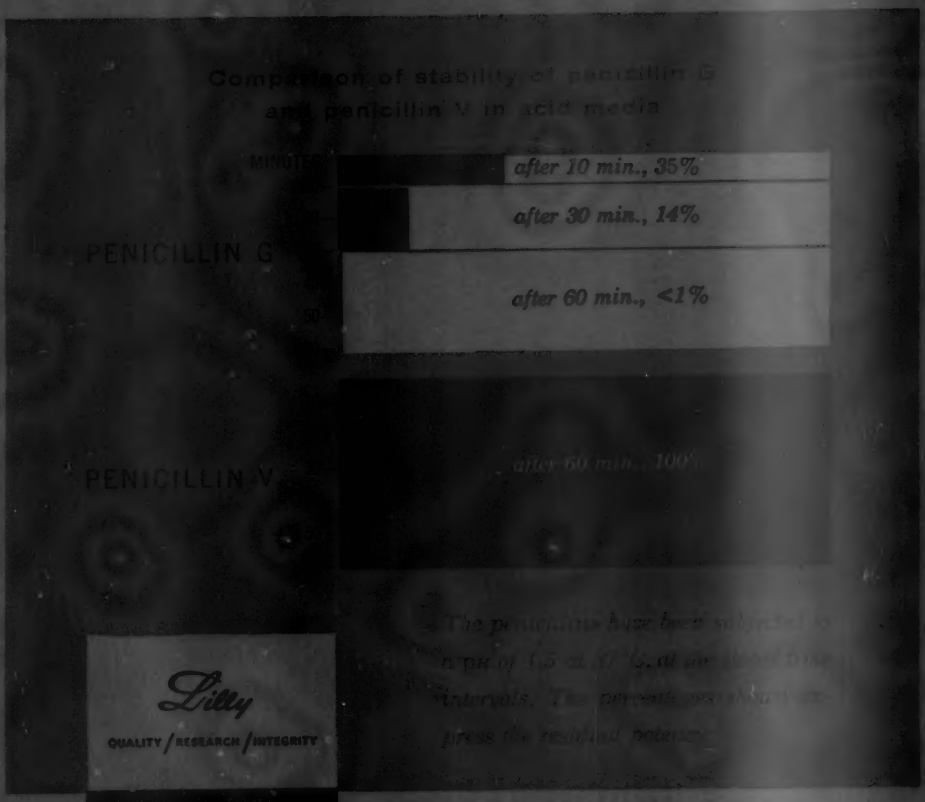
Comparison of stability of penicillin G and penicillin V in acid media
PENICILLIN G
after 10 min., 35%
after 30 min., 14%
after 60 min., <1%
PENICILLIN V
after 60 min., 100%

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(Penicillin V, Lilly)

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